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EDITORIAL

Direct Operations in Tetralogy of Fallot

THE problem before us is that of the best method of treatment of the tetralogy of Fallot. When one is faced with a difficult or controversial problem it is essential to consider first principles.

BASIC PRINCIPLES IN THE TREATMENT OF FALLOT'S TETRALOGY

Although called a tetralogy this condition presents two therapeutic problems: (a) the relief of pulmonary stenosis; (b) the closure of the ventricular septal defect.

One of the fundamental principles of surgery is that a significant obstruction must be relieved. Any departure from this principle must be suspect and for this reason alone the anastomotic procedures are basically unsatisfactory. It is true that it may be a good surgical policy to short-circuit an obstruction by an anastomosis, but the systemic-pulmonary anastomoses of Blalock and of Potts are inadequate in this respect. They are not, for instance, directly comparable with such an operation as gastrojejunostomy, in which the obstructed stomach is drained into the gut beyond. The anastomosis does nothing to relieve the obstructed right ventricle; it merely redirects blood from the aorta to the pulmonary circulation. Even though the immediate, and perhaps the longer term, results of these procedures may be brilliant in correcting cyanosis and disability there is nothing radically corrective in them, and their continued success rests on the slender matter of persistence of an effective artificial ductus arteriosus. The obstruction to the emptying of the right ventricle persists. The proper development and natural growth of the outflow tract is prevented by the fibrous stenosis which becomes relatively more severe as the years pass; in addition, with the daily wear and tear of blood passing through it, the channel becomes smaller, it silts up and thus becomes absolutely as well as relatively smaller. A secondary operation on the outflow tract will encounter this problem of arrested development of the right ventricular outflow even though the pulmonary arteries may have grown larger from the inflow of blood through the artificial ductus.

Thus, in theory, these operations must inevitably reveal themselves as unsatisfactory. My own clinical experience of the results bears this out.

I must first of all emphasize that I intend no criticism of the brilliant pioneer work of Blalock and Taussig and of Potts in their conception and execution of these procedures at a time when nothing else was offered, at a time when no operations were being done on the heart itself. As procedures avoiding direct interference with the heart they were very welcome; today we must assess their value in the light of the historical evolution of direct heart surgery. We all seek only the objective truth.

RESULTS OF ANASTOMOTIC OPERATIONS

From 1947 to 1952 I performed 106 anastomotic operations for Fallot's tetralogy; this excludes operations for tricuspid atresia or for pul-

monary atresia for which an anastomosis is reasonably acceptable and is usually the only feasible method of treatment. The follow-up therefore covers 6 to 10 years. The results are given in Table I.

TABLE I

Blalock's Anastomosis on 106 Patients

Died after operation	14	(32%)
Died since	18	
Survived	92	
Have had second operation	14	(26%)
Need second operation	10	

Result	Initial	Now
Good	81 (76.5%)	41 (40%)
Fair	5	11
Poor	6	17
Not traced		5
Cerebral lesion		12
Subacute bacterial endocarditis		4

Notable are the late deaths which raise the over-all mortality to 32 per cent, and the fact that in 26 per cent of the survivors a second operation is needed. The initial good clinical results in 76.5 per cent of patients has dropped to 40 per cent.

Equally important is the observation that a cerebral lesion (usually an abscess) has occurred in 12 of the survivors, an event which later will be shown to be rare after a direct operation. The reason is easy to see: the non-relief of the pulmonary stenosis means that systemic thrombi or emboli are directed away from the lung into the aorta and thence to the brain. The cerebral lesion serves as a forceful reminder that the basic principle of relief of the primary obstructive process has been ignored. In fact, far from alleviating the ill effects of the ventricular septal defect, an anastomosis aggravates this feature.

It is also necessary to comment that when relapse occurs a very difficult therapeutic problem is encountered. The disabled, cyanosed and grossly polycythemic patient is a very poor operative risk; especially so if any direct operation for relief of the stenosis is used. The heavy collateral circulation makes for severe blood loss at the time of operation, but this can be dealt with. What is often impossible to deal with effectively is the severe postoperative continued bleeding of a fibrinolytic nature which is seen in these bad subjects. It seems especially liable to follow secondary operations after a failed anastomosis.

Direct Closed Procedures To Correct Pulmonary Stenosis

The basic aim of the direct procedures is relief of the pulmonary stenosis either by valvotomy or by infundibular resection, or by a combination of both. I would point out that although nothing is done anatomically to close the ventricular septal defect, nevertheless, a properly performed operation can achieve virtually complete physiologic closure or annulment of the defect. By leaving a certain amount of stenosis the lung circulation is protected from the effects of the ventricular septal defect. In other words, the two circulations are nicely balanced; the right to left shunt is not converted into a large left to right shunt.

Basically, therefore, these operations are founded on a sound surgical principle, namely, the relief of an obstruction. Because they achieve only incomplete relief of the obstruction and still leave the right ventricle beating up against the systemic resistance as well as against a residuum of pulmonary stenosis, they are incomplete and must be improved. There is, however, no doubt that in surgical theory they are superior to the anastomotic procedures.

This superiority is confirmed by a comparable analysis of my own results in 106 direct operations performed between 1958 and 1952, roughly the same period as covered the anastomotic operations presented in Table I. The results are given in Table II.

In contrast to the anastomotic series is seen the smaller cumulative mortality (17 per cent as opposed to 32 per cent), and the lower incidence of relapse (13 per cent as against 26 per cent). Also, the initial clinical good result in 73 per cent of cases is reasonably maintained at 64 per cent.

TABLE II
Direct Operation on 106 Patients

Died from operation	16	(17%)
Died since	2	
Survived	90	
Have had second operation	7	(13%)
Need second operation	5	

Result		
	Initial	Now
Good	78 (73%)	68 (64%)
Fair	12	6
Poor	1	11
Cerebral lesion		1
Subacute bacterial endocarditis		1

It is to be noted that a cerebral lesion occurred in only one patient and, very significantly, in this case the clinical result had been poor owing to incomplete relief of the stenosis. In other words, the right to left shunt had not been corrected enough to prevent paradoxical embolism.

These figures should prove once and for all that direct relief of the pulmonary stenosis can be achieved with good results and with a reasonably low mortality. They emphasize that these operations must be soundly conceived both anatomically and technically in so far as their limitations allow. I have no space here, nor indeed desire, to argue out yet once more the fact of their sound anatomic conception; this I consider is now sufficiently proved and accepted. I almost despair to hear comments still made that these direct operations are wrong in principle and dangerous in execution; an observation I had to listen to as recently as several months ago at an important surgical meeting in London!

The result is inevitably imperfect after some of these direct procedures; sometimes the relief of stenosis is inadequate; occasionally, it may be excessive and the lungs are flooded. Neither of these things happens often. However, I hold no brief for continuance of these direct closed operations in preference to a total open corrective procedure if such can be satisfactorily achieved. Indeed, even when a nice balance of the two circulations has been obtained and the patient is clinically free from cyanosis and disability and outwardly appears to have an excellent functional result, it cannot be claimed that all is well. The right ventricle is still carrying a burden in regard to the partial pulmonary stenosis which remains and in regard to the systemic resistance against which it must beat. This burden is usually reflected in the electrocardiogram which tends to show an increasing right ventricular strain pattern as the years pass.

No thinking person can have confidence that this is a satisfactory state of affairs, and the need for closure of the ventricular septal defect becomes clear. Until recently this has not been possible technically, and even now with the advent of open heart surgery under total body perfusion it has proved unsatisfactory in a disturbingly high proportion of cases. The high mortality encountered has given pause to many plans for routine total corrective surgery in Fallot's tetralogy. Before going on to analyze this problem more fully it is necessary to make a few more comments on the direct procedures.

In discussing the anastomotic operations it was emphasized that nothing is done to relieve the actual stenosis of the pulmonary outflow, which in addition to remaining small also silts up and becomes narrower as the years pass. One outstanding advantage of the direct operations is that by relieving the stenosis the whole pulmonary outflow tract is allowed to open up and carry more blood to the lungs by the natural pathway and to grow and to develop naturally as the years pass. This is an absolutely fundamental conception in the assessment of the value of the direct operations and is fundamentally linked with the success or failure of one-stage correction.

Total Correction of the Lesion

No thinking person will question the desirability of one-stage total correction of the basic abnormalities in Fallot's tetralogy, namely total relief of the pulmonary stenosis and closure of the ventricular septal defect. That this can be achieved with success has been brilliantly shown by Lillehei and by Kirklin and by other surgeons.

What concerns us today is the high mortality which accompanies these operations. The mortality of the Minneapolis group has been recently given as between 45 and 50 per cent, leading Blalock to point out that with such a high fatality rate the term "total curative procedure" should be modified to "total corrective procedure." The Mayo group also has an overall mortality not much below this although the more recent figures show a great improvement. Most other surgeons have had an even higher mortality. In my own small series the mortality has been 75 per cent.

Wherein therefore lie the drawbacks to total correction; why should the mortality be so high?

The reasons are not far to seek. They are related to expecting too much in applying a standard type of total operation to a disease condition in which there is a whole range of morbid anatomy—from severe stenosis with a large septal defect, great disproportion between the aorta and the pulmonary artery and with a commensurate large right and small left ventricle, to cases in which the stenosis is milder with little disproportion between the aorta and the pulmonary trunk and the ventricles are more evenly matched. Surgeons have attacked these cases by a general standard technic with no finesse and no conception of respect for the varying circulatory adjustments needed after total operation; hence, the high failure rate and lessened confidence.

If these corrective operations are to continue, as continue they must, much more circumspection is needed in the selection of the type of operation for each individual case.

I would emphasize that in our homage paid to the recent great technical advances in operative treatment of heart diseases by the successful introduction of total perfusion, we must take care not to overlook the need for observance of good surgical principles; no technical advances can afford to ignore these.

Surgeons have been quick to appreciate that many of the failures are due to inability to relieve the pulmonary stenosis sufficiently radically; that patients may enter the postoperative phase with residual pulmonary stenosis. Where the stenosis is well relieved the results are good; when stenosis persists the mortality is high.

How has this been faced? The present popular policy is to try and enlarge the outflow tract by sewing into it a patch of Ivalon or some such material. In this way the pulmonary outflow is enlarged and the immediate postoperative problem of residual stenosis may be circumvented. This cannot be a permanently satisfactory step. The whole of our surgical experience should deflect us from the use of foreign substances which sooner or later always give trouble. This is so even in a comparatively quiet part of the body in which these substances are free from stress. To introduce them deliberately into such a constantly and powerfully functioning area as the outflow tract of the right ventricle seems to me to be courting disaster. Still worse, when the pulmonary trunk itself is small it is the custom to sew a prosthesis across the pulmonary valve (thereby causing regurgitation) and into the pulmonary trunk itself. The severe mechanical stresses to which such a patch is subjected must be unfavorable, quite apart from the unjustifiable ignoring of the effects of pulmonary regurgitation. At the risk of being thought reactionary I must take a firm stand against such a surgical policy, so ill conceived.

But there is still more to the problem than this. The plastic widening of the pulmonary outflow presupposes that the postoperative disability lies in it alone. The ventricular functions are ignored.

A high grade pulmonary stenosis with a small outflow tract does not stand alone; with it is associated a disproportion between the two ventricles as is shown clinically, radiologically, by electrocardiogram and by observation at operation and at postmortem. The large right ventricle in these cases must be supporting much of the systemic circulation, a function which it has taken over from the diminutive left ventricle. When the septal defect is closed the right ventricle no longer supports the systemic circulation and the left ventricle may be incapable of doing so alone; failure is inevitable in many cases.

The Two-Stage Procedure

How then can we face this problem of a small pulmonary outflow, a powerful right ventricle

and a too small left ventricle in the more severe cases of the Fallot type? I suggest that we should allow Nature to help; that we should give her a chance to adjust the balance more gently and not to force her hand overnight. This can be achieved by a two-stage procedure. The first should be a simple relief of the pulmonary stenotic element either by a closed or (if preferred) by an open operation; I feel a closed operation has certain advantages. In this way the whole pulmonary outflow tract can develop and grow to an adequate size. In addition, readjustment of the two circulations will lead to readjustment of the relative functions of the two ventricles; the left ventricle will take over a larger share of work. Later the ventricular septal defect can be closed under potentially safer conditions.

I am aware that this involves two operations with a possible higher total mortality. It has as yet not been shown that the combined mortality will necessarily be higher than a poorly conceived primary total correction as at present performed. Also, we must remember late mortality from troubles occurring in plastic substances sewn into the pulmonary outflow. Time alone will supply the answer.

I put forward as a practical suggestion that a place still remains for continuance of the direct operations for relief of the pulmonary stenosis without primary closure of the septal defect for certain severe cases of Fallot's tetralogy. That a two-stage procedure is needed in some cases is clearly also the opinion of many others, for we hear advocacy of returning to an anastomotic procedure as a first stage operation. This cannot be a sound move; for the reasons already given it fails in the most important particular of encouraging growth and development of the pulmonary outflow tract of the right ventricle proper.

Selection of Surgical Procedure

How should we select cases for a one-stage or for a two-stage operation? I suggest the following criteria should point to the wisdom of a preliminary relief of the stenosis alone:

(1) Patients under (arbitrarily) two years of age.
(2) Severe cyanosis or disability.
(3) Severe polycythemia.
(4) Severe pulmonary stenosis
  (a) clinically
  (b) by plain radiography
  (c) by angiocardiography
(5) A large aorta (by inference the pulmonary outflow is inversely small).
(6) ECG evidence of a very large right ventricle.
(7) ECG evidence of a small left ventricle.

In the final event the decision may be deferred until thoracotomy; thus provision must be made for total heart-lung bypass, but if the conditions appear unfavorable this need not be used if a simple closed operation on the stenosis seems indicated.

Only time will tell in how many of these a second operation is needed and with what ultimate success. That the direct procedures can lead to satisfactory growth of the whole pulmonary outflow from a diminutive to a normal size is quite certain, for I have observed it in many cases.

Sir Russell Brock
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Clinical Study

The Surgical Correction of Aortic Regurgitation

Bicuspid Conversion*

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DURING the past seven or eight years, much thought and effort have been devoted to the problem of incompetence of the aortic valve. Essentially, this condition amounts to an aorticoventricular fistula. In general, three lines of attack have been employed. In the first, an attempt has been made to replace the loss of valvular sufficiency by *implantation of a prosthetic appliance* either in the region of the normal valve or farther on in the arterial line.[1-4] Of these technics, only the method of Hufnagel,[2,5] in which a prosthetic ball valve is inserted into the continuity of the descending thoracic aorta (Fig. 1), has enjoyed a significant measure of clinical acceptance.

The second method or approach has consisted of efforts to "narrow" or "constrict" the dilated aortic "ring" [6-9] by the tightening of a *circumferentially placed "sash" or suture*. These efforts have come to naught chiefly because there is no anatomic structure at the root of the aorta in the human heart which might properly be called an annular ring (Fig. 2).

The third general method includes *various plastic procedures* in which the valve structures are attacked or modified directly. With the exception of a few early and abortive attempts at implantation of pedicled tissues into the aortic lumen[1] and external suturing or plication of the aortic root,[7] the development of these plastic operations has depended upon direct visualization of the valve by an open technic, usually with total cardiopulmonary bypass (Fig. 3). In our own clinic, due to the efforts of Blanco,[10,11] an extracorporeal circulation, in which both sides of the heart are bypassed but the patient's

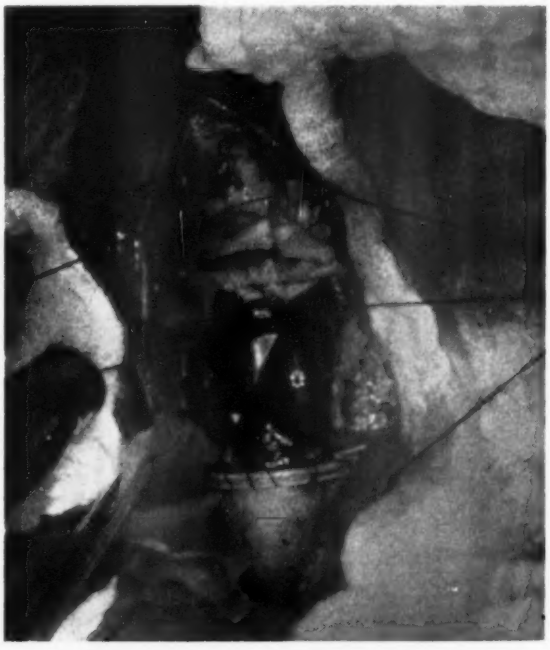

Fig. 1. Photograph of Hufnagel plastic ball-valve after insertion into the continuity of the descending thoracic aorta.

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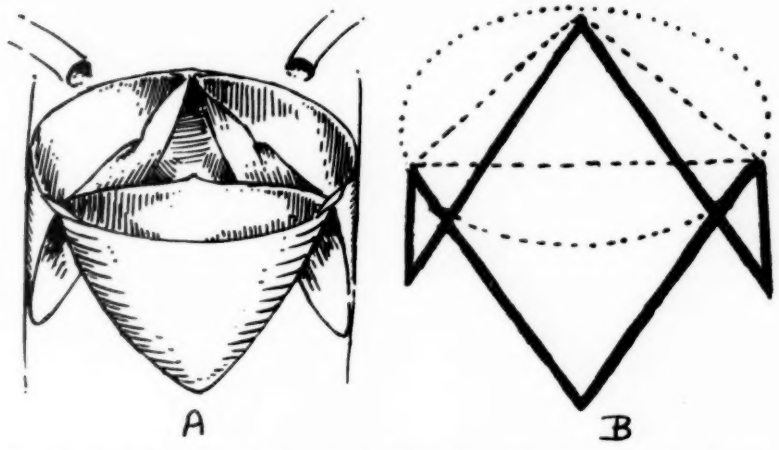


Fig. 2. (A) Diagrammatic representation of the aortic valve cusps showing the absence of any structure in this area which properly might be referred to as an annulus fibrosus. (B) Zigzag fibrous line of attachment of the cusps to the aortic wall. Such a structure provides no reinforcement against dilatation of the aortic root.

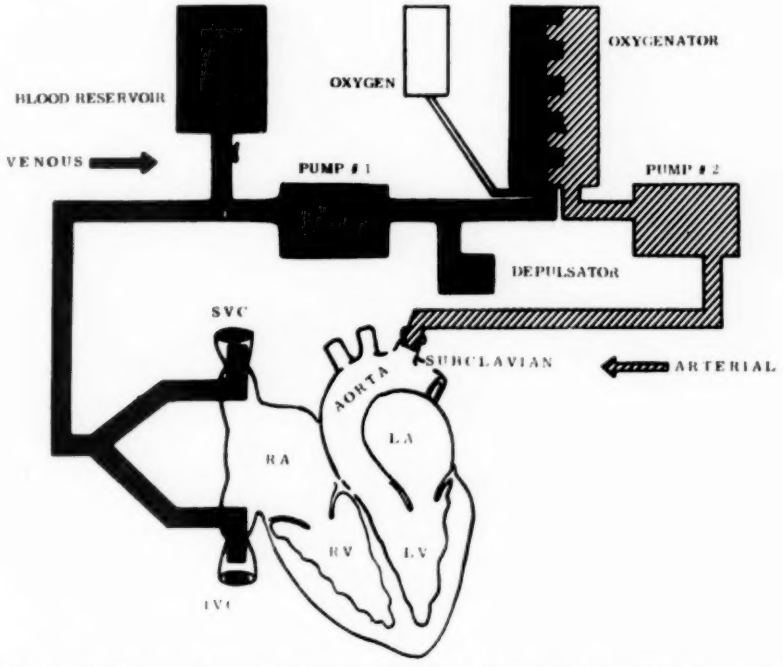


Fig. 3. Diagrammatic representation of hook-up of essential elements in the usual "total" cardiopulmonary bypass procedure.

own lungs are used for oxygenation, has seemed preferable (Fig. 4).

Bicuspid Conversion of the Aortic Valve: Since fully acceptable prosthetic devices, as yet, have not been devised for insertion at the aortic valve level, and since application at any later point in the circulation is grossly unphysiologic, and in view of the fact that circumferential constriction of the aortic root has been disappointing, we have come to employ the method of direct open attack upon the valve structures in nearly every type of aortic insufficiency. As a result of our experience with some 80-odd cases of aortic valve pathology operated upon by an open technic, one rather astounding conclusion has been reached: With the exception of instances

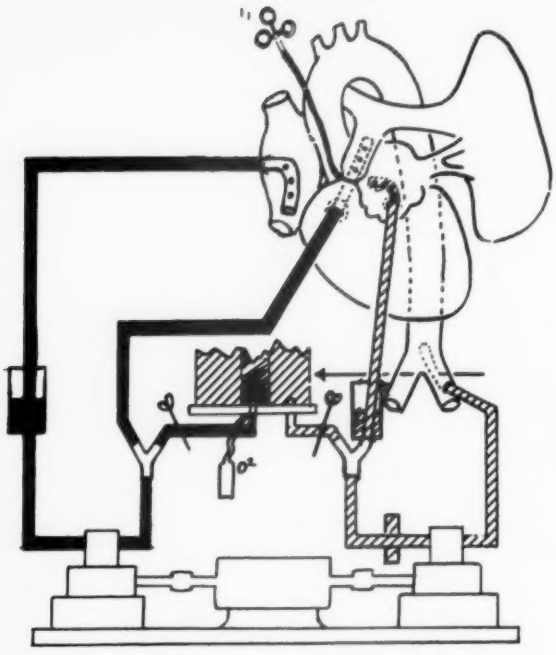


Fig. 4. Blanco's method of simple cardiac bypass in which the patient's own lungs are used for oxygenation. Arrow points to an auxiliary oxygenator of the bubble type connected in parallel for possible emergency use. Prolonged bypass is permissible with this type of extracorporeal circulation since it is the oxygenator rather than the pumps which causes most of the damage to the blood elements.

of predominant aortic stenosis in which surgical "thinning" of the valve by a "sculpturing" technic may bring about sufficient "lengthening" of the cusps to lessen or overcome an associated less significant element of aortic incompetence, correction of aortic regurgitation necessitates the surgical conversion of the in-

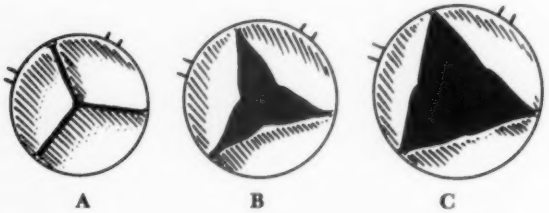


Fig. 5. (A) Normal relationships of aortic cusps to arterial circumference. (B) In "pure" aortic insufficiency the artery becomes dilated so that even completely normal cusps become unable to defend the enlarged passageway. (C) In extreme dilatation of the aortic root the free margins of the cusps become "stretched-out" like geometric chords which subtend 120° arcs of the circular passageway.

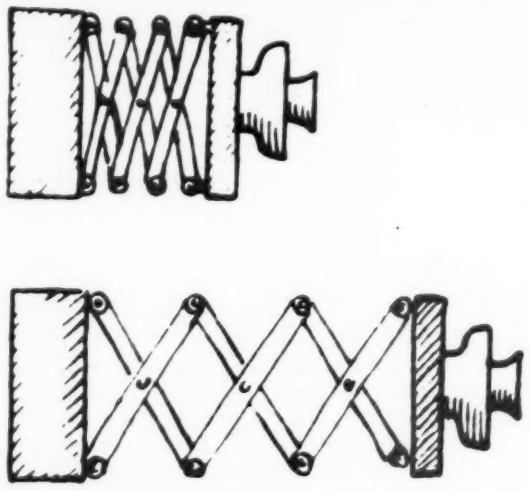


Fig. 6. Old fashioned office extension telephone bracket. Note that the rigid zigzag members offer no resistance to extension. Compare with Fig. 2B.

competent *tricuspid* valve structure into a *bicuspid* one. The explanation for this is many-faceted, but may be simplified (or oversimplified) by saying that a bicuspid valve inherently is structurally much stronger (in defending against incompetence) than a tricuspid one.

Types of Valve Deformity in Aortic Insufficiency: It is also essential to realize at the start that, except in cases of frank congenital malformation or trauma, there are but three common types of acquired aortic valve deformity which lead to aortic regurgitation. In the first form ("pure insufficiency"), the aortic root becomes dilated to such an extent that completely normal cusps are unable to defend the enlarged passageway (Fig. 5). It should be noted that there is an aortic root, but no aortic ring, at least not if one retains the usual concept of an annular structure similar to that of a wedding band. The only continuous structure of fibrous character which can be found in the first portion of the aorta, as one of us (J. Z.) has shown, is the zigzag line of attachment of the aortic cusps to the arterial wall (Fig. 2). Such an architectural element provides no more resistance to dilatation of the aortic wall than does the usual office telephone extension bracket to linear elongation (Fig. 6).

The second type of aortic insufficiency is that caused by prolapse, inversion, or retraction of one or more of the valve cusps (Fig. 7). For-

tunately, one (or two) of the cusps usually retains its normal configuration and is capable of supporting itself and this renders effective surgical correction feasible.

Fig. 7. Prolapse of an aortic valve cusp causing incompetence. (From Bailey and Imbriglia[11]; Courtesy of Charles C Thomas Co., Springfield, Ill.)

In the third type of aortic regurgitation, the pathology is basically that of rheumatic thickening and shortening of the cusps, with a variable amount of commissural obliteration. Frequently, an appreciable element of stenosis coexists with the regurgitation. Consequently, the surgical procedure must be one which is designed to correct all factors which contribute to the valvular dysfunction.

"Pure" Aortic Insufficiency

Whether this condition is caused by luetic aortitis, Marfan's disease, rheumatic valvulitis, or one of the several other conditions which can bring about dilatation of the aortic root, the physiologic disability derives from the inability of the aortic cusps, which remain more or less normal in structure, to meet in the center of the enlarged vascular passageway. Consequently, a central triangular "aperture of incompetence" exists during diastole. Should the aortic dilatation become extreme, the free margin of each cusp will become "stretched out" as a geometric chord subtending an arc which amounts to one-third of the perimeter (120°) of the circular passageway (Fig. 5).

Experiences with "Annular" Constriction: Originally, it had seemed to one of us[6,7] that "annular" constriction by a circumferentially placed "sash" of plastic fabric would so reduce the aortic aperture as to permit coaptation of the valve cusps and thus overcome the incompetence. Indeed, it often was possible to raise the diastolic blood pressure by this technic and to alter the arterial pressure tracing in the direction of normalcy (Fig. 8). Unfortunately, such sashes ultimately

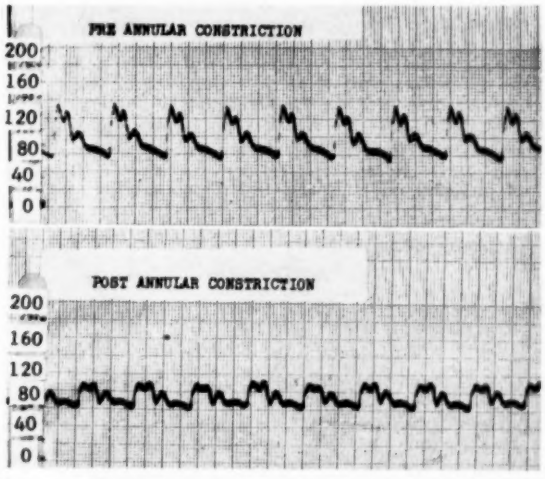


Fig. 8. Brachial arterial tracing (upper) obtained in patient with free aortic insufficiency prior to tightening of "circum-annular" sash. Alteration in brachial arterial tracing (lower) following tying-down of sash.

"cut through" or become displaced into the ventricular or arterial lumen with consequent loss of constriction, and sometimes with superimposition of subacute bacterial infection. Of 30 such patients so operated on by the senior author[6,7,8] over a two-year period which was terminated in mid-1955, all but two are now dead.

Concept of Bicuspid Conversion: Anatomic dissection having revealed the lack of a true aortic "annulus fibrosus" and the existence of the previously mentioned zigzag line of cusp attachment, thought was given to plication of this line. The concept of bicuspid conversion with functional (but not necessarily actual) elimination of the noncoronary cusp was developed. In the experimental laboratory it was readily demonstrable that such bicuspid conversion could be accomplished and that the resulting valve structure tended to be fully sufficient (Fig. 9). It was apparent that such a bicuspid valve presented

great advantages over a tricuspid one with respect to competence. The free margins of the remaining cusps naturally tend to assume the position of parallel and contiguous diameters of the reduced circular passageway. Not only is

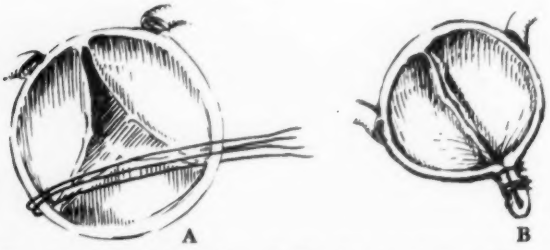


Fig. 9. (A) Application of plicating mattress sutures through the two commissures which mark the extremities of the noncoronary cusp. (B) After tying down these sutures (and obliterating the sinus of Valsalva completely with additional sutures) the incompetent tricuspid aortic valve will have been converted into a competent bicuspid one. The free margins of the remaining cusps now represent parallel (and contiguous) diameters of the reduced circular passageway.

the structural strength of such an arrangement obvious, but even further dilatation of the aortic root would not disturb it. No doubt such a valve would offer some additional element of impedance to the free flow of blood, but the clinical benignity of congenital bicuspid formation of the aortic valve suggests that such an effect would be slight.

Case Histories

Case 1. On July 19, 1956, D. E. (#56-23165), a 46-year-old white man with an old history of lues and severe aortic regurgitation (BP 200/50/0), was operated on at the Hahnemann Hospital. Using a transverse submammary incision, the circulation was bypassed with a heart-lung apparatus and retrograde perfusion of the coronary sinus. The widely dilated ascending aorta was incised longitudinally and the valve was visualized. The cusps appeared to be normal in structure and flexible. The noncoronary cusp was plicated at the level of the commissures with interrupted mattress sutures of heavy silk. The aortic incision was closed with two rows of running sutures.

Shortly after the circulatory perfusion was terminated, cardiac action having become vigorous, bleeding was noted from the region of the plicating sutures, one of which apparently had cut through the aortic wall, perhaps as a result of the rather violent pulsatile excursions characteristic of this portion of the aorta. During efforts to suture the aortic laceration much blood was lost. Ventricular fibrillation occurred and proved irreversible.

Case 2. On March 7, 1957, an aortic plication operation was carried out at the Hahnemann Hospital upon E. S. (#57-30498), a 32-year-old white male with predominant aortic insufficiency (BP 170/40/0), using total cardiopulmonary bypass with a double Sigmamotor pump and a Friedland-Gemeinhardt bubble type oxygenator. The coronary sinus was cannulated for retrograde perfusion. The commissures of the noncoronary cusp were approximated with interrupted mattress sutures of heavy silk. At the conclusion of the definitive procedure, the aortic wall was repaired with two continuous rows of 4-0 arterial silk, one of mattress and one of simple type. The blood pressure assumed normal proportions (BP 120/80) and a palpable shock of aortic valve closure became apparent.

The patient reacted well, but three and one-half hours after operation suddenly went into shock with evidences of internal bleeding. Reoperation disclosed that the aortic suture line had cut through in two separate areas, permitting massive bleeding. Efforts to repair the aortic wall failed and the patient expired.

Case 3. On March 27, 1957, R. C. (#57-32466), a 43-year-old white male with predominant aortic insufficiency (BP 170/20/0), was subjected to plication of the noncoronary aortic cusp at the Hahnemann Hospital using total cardiopulmonary bypass with a heart-lung apparatus and retrograde perfusion of the coronary sinus. The noncoronary cusp was "eliminated" by cross-plication at the level of the commissures. Buffering pledgets of Ivalon sponge were incorporated within the plicating sutures and also the aortic suture line of closure. However, the heart appeared to be incapable of "taking over" the total circulation, developing ventricular fibrillation each time the pump was discontinued. Eventually the fibrillation became irreversible.

Case 4. On May 21, 1957, E. P. (#57-34559), a 37-year-old white male with severe aortic insufficiency (BP 140/40/0), was similarly operated on at the Hahnemann Hospital using the heart-lung machine and potassium citrate arrest. The line of aortic sutures was reinforced with buffering strips of Ivalon sponge. None of the aortic wall was excised, neither was the "eliminated" noncoronary cusp. It was noted that the aortic valve cusps were somewhat thickened and shortened with "rolling-in" of their free margins; hence, even after "bicuspid conversion," the approximation of the remaining two cusps was not perfect.

We were not surprised, therefore, that a perfect result was not obtained. The blood pressure rose to 130/60 and a good aortic 2nd sound became audible. However, an early blowing basal diastolic murmur has persisted. The patient was much improved clinically and remains so to the present time. There has been a gradual lowering of the diastolic blood pressure although not to the original low level suggesting that the effect of the plication might partially have been lost, perhaps due to cutting through of the effective sutures.

Case 5. E. P. (#57-35195), a 36-year-old white

female with severe aortic insufficiency (BP 150/20/0), was operated on at the Hahnemann Hospital on June 4, 1957, using complete cardiopulmonary bypass for the aortic procedure. Fifty cubic centimeters of 3% potassium citrate solution was used to produce cardiac arrest. The noncoronary cusp and corresponding sinus of Valsalva were obliterated by plication with heavy silk mattress sutures passed through buffering pledgets of Ivalon sponge. The aortic suture line of closure also was placed through buffering strips of Ivalon sponge.

Postoperatively the patient has done extremely well although a grade 1 diastolic basal murmur persists. Her blood pressure has assumed normal levels (Fig. 10)

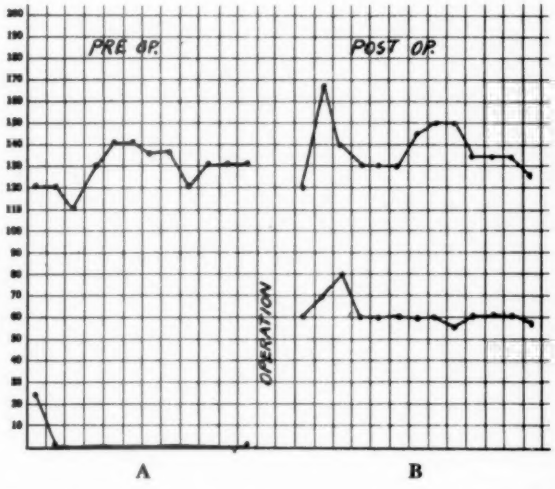


Fig. 10. Case 5. (A) Preoperative blood pressure chart in a 36-year-old white woman with "pure" aortic insufficiency. (B) Postoperative blood pressure chart following bicuspidization of the aortic valve. It is believed that her valvular incompetence has been corrected practically completely.

and it is felt that her aortic incompetence is nearly completely abolished. Clinically she is doing very well.

Case 6. On July 18, 1957, L. W. (#57-37076), a 22-year-old white male with severe aortic insufficiency (BP 150/0), was operated on at the Hahnemann Hospital. A complete cardiopulmonary bypass was employed using a pump-oxygenator and potassium citrate arrest. The noncoronary cusp and the corresponding sinus of Valsalva were eliminated by plicating sutures passed through pledgets of Ivalon sponge. The cardiac action was restored satisfactorily and the blood pressure in the operating room was obtained at 120/80 mm Hg. The shock of aortic valve closure was readily palpable. However, shortly after return to the recovery room, ventricular fibrillation developed and proved irreversible.

Case 7. On January 26, 1958, A. J. (#58-43842), a 52-year-old white male with severe aortic insufficiency (BP 160/30/0), was operated on at the Hahnemann Hospital. Total cardiopulmonary bypass and potassium citrate arrest were employed. The noncoronary cusp was obliterated by plication, not only of the commissures, but also of the line of attachment of the cusp to the aorta as well. He now is in good clinical condition with a blood pressure of 130/60 and a good aortic 2nd sound. However, an early soft blowing diastolic murmur still may be heard (Fig. 11).

Case 8. On March 19, 1958, at the Hahnemann Hospital, operation was done on H. B. (#58-45789), a 58-year-old white female with a widely dilated (practically

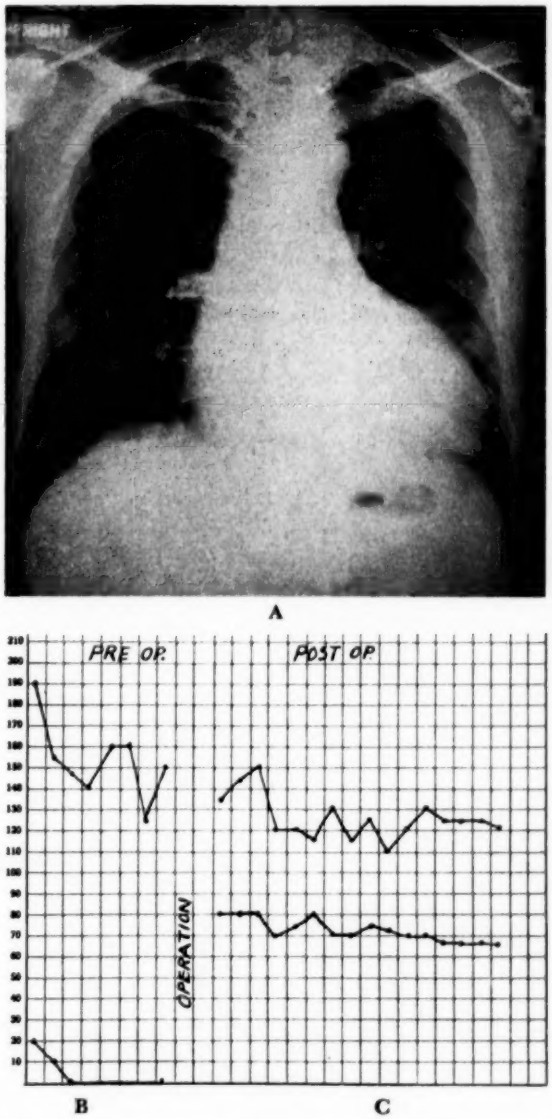
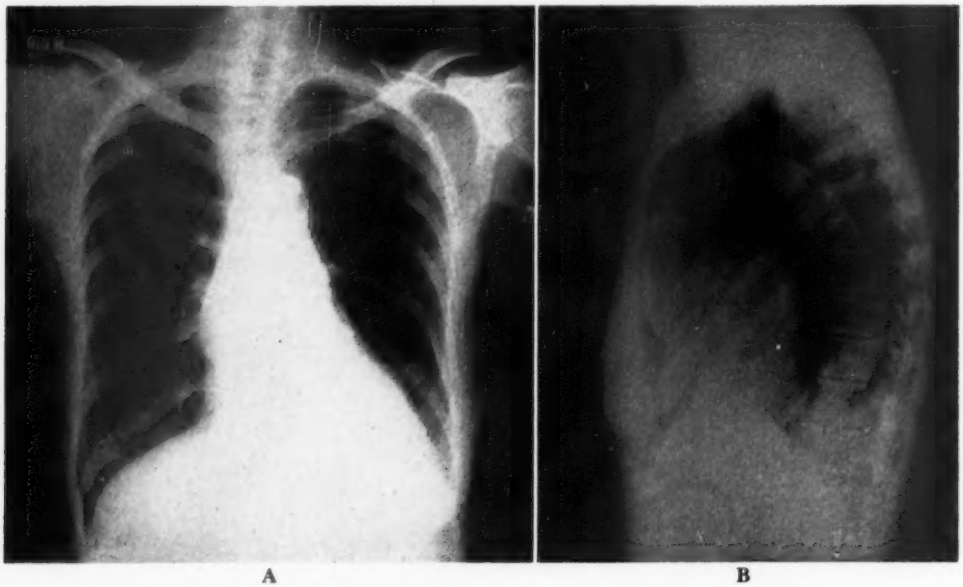
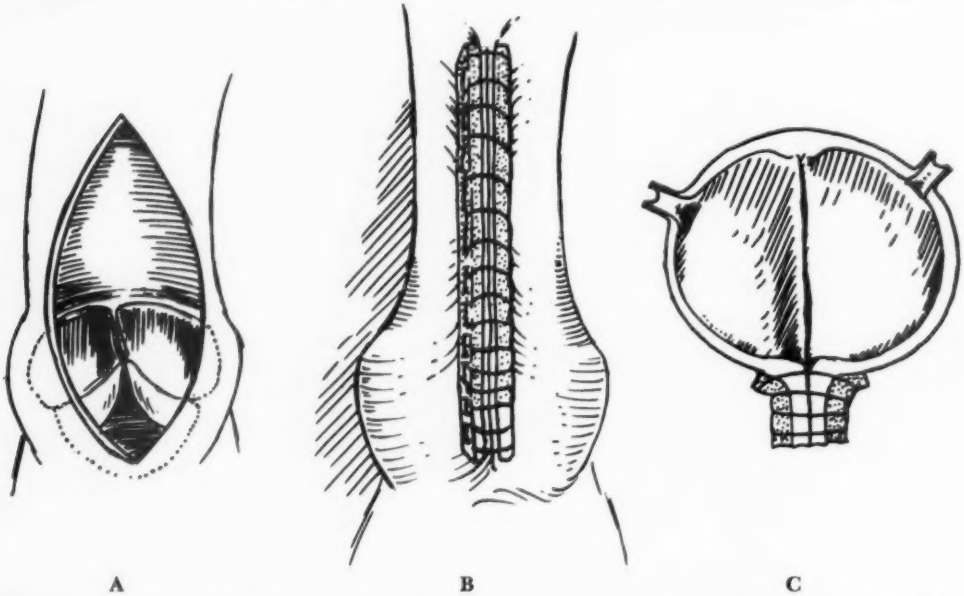


Fig. 11. Case 7. (A) Enlarged boot-shaped heart in A. J. who was suffering from "pure" aortic insufficiency. (B) Preoperative blood pressure chart showing very low diastolic blood pressure level. (C) Elevation of diastolic pressure following bicuspidization of the aortic valve.



A B

Fig. 12. Case 8. (A) P. A. roentgenogram in a 58-year-old white female with fusiformly dilated (and calcified) ascending aorta and severe valvular insufficiency. (B) Lateral roentgenogram.



A B C

Fig. 13. Case 8. (A) Diagrammatic representation of large elliptical excision of portion of the wall of the ascending aorta including the noncoronary sinus of Valsalva. The noncoronary cusp was excised but its fibrous line of aortic attachment was preserved. (B) Outline of repaired aortic wall, the approximating sutures having been placed through buffering strips of Ivalon sponge. Note restoration of normal narrowing at a level just beyond the remaining sinuses of Valsalva. (C) Sectional view showing bicuspidization (and restored competence) of the aortic valve.

aneurysmal) ascending aorta (Fig. 12). She presented every evidence of advanced heart failure and full blown aortic insufficiency (Corrigan pulse, imperceptible diastolic blood pressure). Total cardiac bypass using the autogenous lung and potassium citrate arrest was used. An ellipsoid of aortic wall measuring 8 cm in length by 4 cm in its greatest width was excised including practically the entire noncoronary sinus of Valsalva. The noncoronary cusp was largely detached from the aortic wall but was sutured in such a manner as to reinforce the right coronary cusp which was somewhat damaged. The aortic wall defect was repaired using a

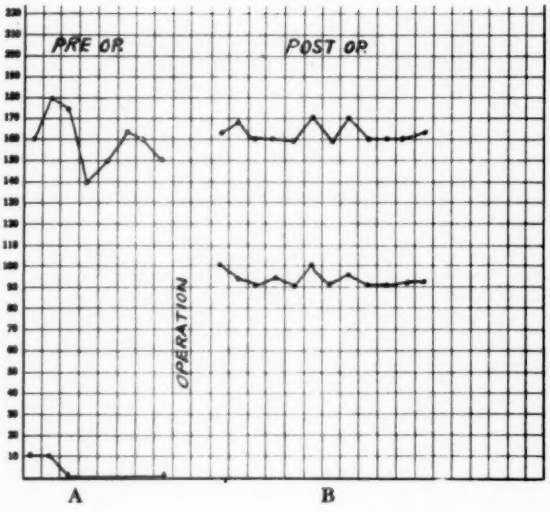


Fig. 14. Case 8. (A) Preoperative blood pressure chart showing very low diastolic levels. (B) Postoperative blood pressure chart following bicuspidization of the aortic valve. It is believed that full valvular competence has been restored.

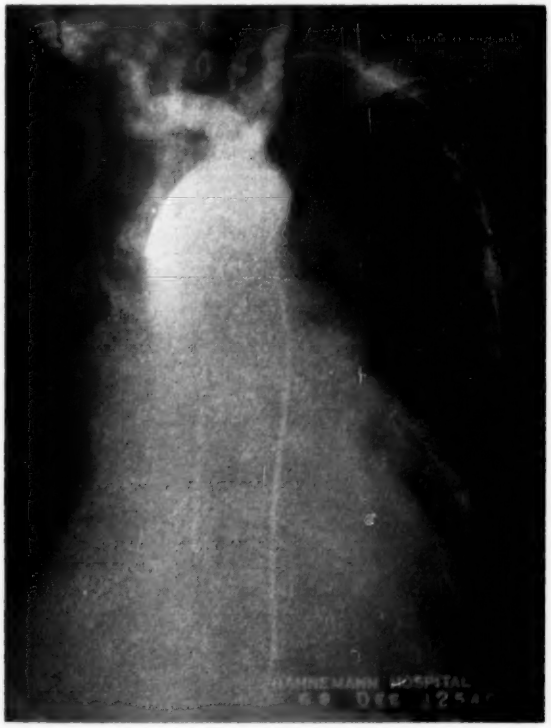


Fig. 15. Case 8. Postoperative aortogram. Catheter introduced via the right femoral artery into the supravalvular region. The central opacification is from a Steinman pin used to approximate the edges of the sternum.

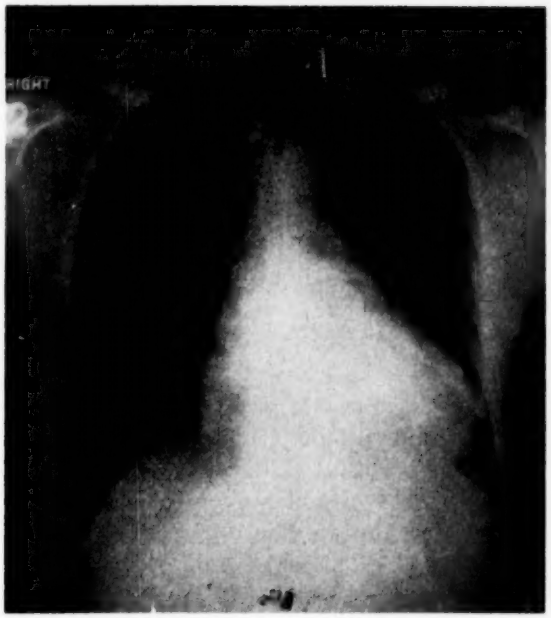


Fig. 16. Case 9 Enlarged heart shadow of a 36-year-old white male with severe aortic insufficiency.

double row of approximating sutures passed through buffering strips of Ivalon sponge (Fig. 13). The technical aspects of the repair were rendered especially difficult by the presence of extensive calcific plaques within the aortic wall. The period of total circulatory bypass was two hours and twenty minutes in this case.

Postoperatively the patient has done extremely well, apparently being cured completely of her aortic regurgitation (Fig. 14). The postoperative aortogram fails to reveal any opacification of the left ventricle (Fig. 15). The diastolic murmur has been abolished and a 2nd aortic sound of normal magnitude has returned.

Case 9. On April 18, 1958, C. Di B. (57-35196), a 36-year-old white male with severe aortic insufficiency and a large heart (Fig. 16), was operated on at the Hahnemann Hospital using total cardiac bypass with the autogenous lungs for oxygenation, and direct coronary arterial perfusion with catheters (Fig. 17). An ellipsoid of aortic wall including the noncoronary sinus of Valsalva was resected. The noncoronary cusp was not physically excised. The aortic wall was repaired in the usual manner using Ivalon buffered interrupted silk sutures to approximate the commissures of the eliminated cusp.

The patient reacted well and has had a normal blood pressure curve since operation (Fig. 18). A grade 1 early blowing diastolic murmur may be heard along the left margin of the sternum, suggesting the persistence of a minor element of aortic incompetence. However, his condition approaches a clinical cure.

COMMENT

From these experiences it was concluded that

in simple plication of the commissures and in simple suture repair of the aorta there was a significant risk of acute cut-through and hemorrhage. Moreover, even with suture obliteration of the "excluded" and plicated sinus of Valsalva permanent correction of the incompetence might not be provided due to the possibility of gradual cutting through of the sutures with reconstitution of much of the original arterial passage. Furthermore, it was felt that narrowing of the lower aortic passageway with maintenance of a normal-sized lumen above the cusps might interfere with the normal mechanism of coronary perfusion since the natural (relative) postvalvular narrowing of the aortic lumen probably converts a portion of the aortic end-pressure into lateral pressure which distends the sinuses of Valsalva (Fig. 19). Hence, it was decided that a large enough elliptical piece of aortic wall should be excised to permit significant narrowing of the postvalvular arterial lumen. Moreover, it was felt that the excised area should include the noncoronary sinus of Valsalva but that it should not be extended beyond the limits of attachment of the noncoronary cusp. It now is felt that the noncoronary cusp should be excised physically.

It is interesting to note that Garamella and associates,[13] in November, 1957, described a similar technic which they have applied ex-

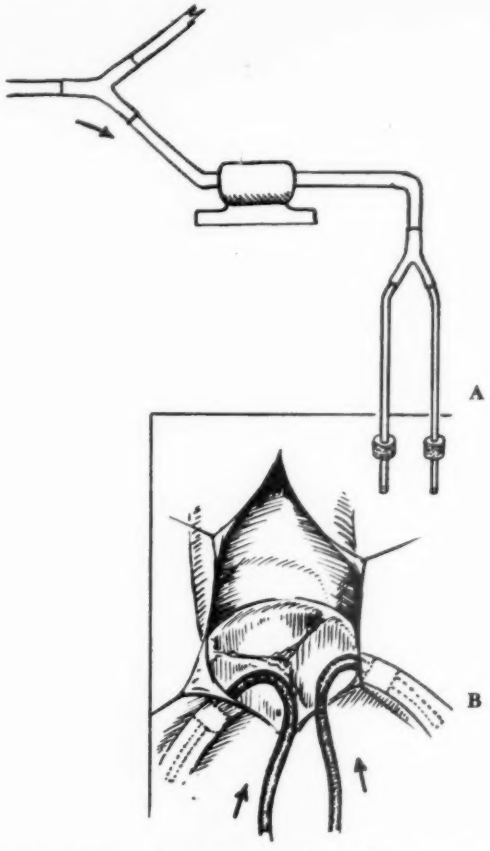


Fig. 17. Case 9. (A) Sponge rubber cuffed polyethylene tubes used for perfusion of the coronary ostia. (B) After the cuffs have been inserted fully into the coronary arteries mattress sutures of fine silk are used to tighten the inner aortic wall about the ostia.

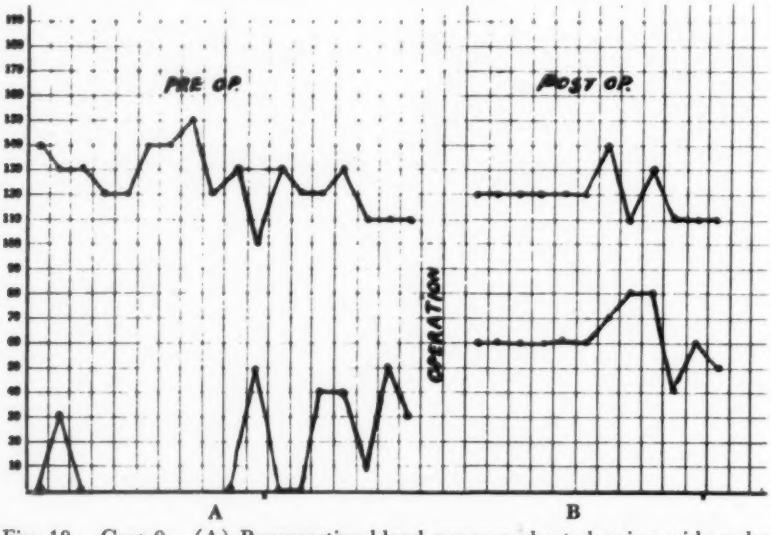


Fig. 18. Case 9. (A) Preoperative blood pressure chart showing wide pulse pressure. (B) Narrowing of pulse pressure and elevation of the diastolic level following bicuspidization of the aortic valve. It was felt that a small element of valvular incompetence remained.

perimentally. They believe that physical excision of the noncoronary cusp is preferable to defunctionalization by plication. Unknown to the authors at the time, Cooley and associates[14] had conceived a similar approach to the problem of "pure" aortic insufficiency and have reported two unsuccessful clinical attempts at the September, 1957, meeting of the American College of Surgeons. Creech[15] has operated (August 8, 1957) a similar case with survival.

While four of our nine patients have failed to recover in this effort to develop an effective and feasible operation for "pure" aortic insufficiency, it is felt that as a result of this experience deaths from similar causes may be prevented in the future. Certainly, aortic suture line disruption can be avoided by the use of buffering strips of Ivalon sponge. Presumably, the improved myocardial nutrition resulting from direct perfusion of the coronary arteries during the course of the operation will enable many of these overstrained and exhausted hearts to withstand the stress of surgery.

It now is felt that the noncoronary sinus of Valsalva should be physically resected in order to obviate the possibility of subsequent reconstitution of the original arterial lumen. Furthermore, it is deemed essential, in order to insure normal coronary perfusion, to excise sufficient of the postvalvular portion of the aortic circumference to restore a normal amount of narrowing of the lumen at this level. Whether the noncoronary valve cusp actually should be excised, or whether functional obliteration by plication is sufficient, has not been determined definitely. At the present time, we favor its excision.

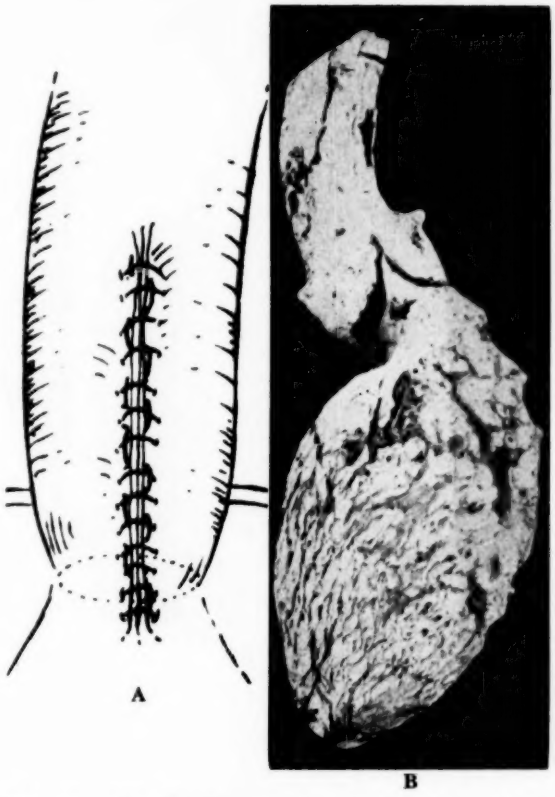
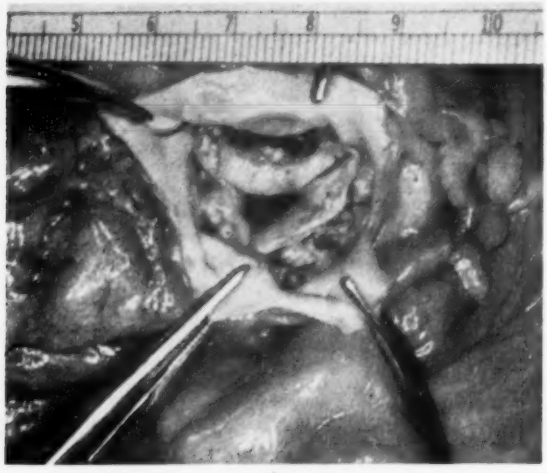


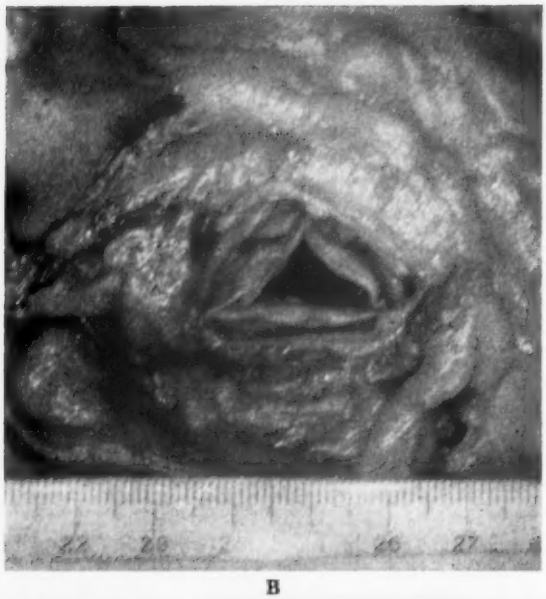
Fig. 19. (A) Plication of the aortic valve without excision of aortic wall tissue produces an abnormal relationship with the postvalvular portion of the aorta which may impede coronary filling. (B) In contrast, as shown in this latex cast, the aortic passageway normally is narrowed at a level above the sinuses of Valsalva, an arrangement which favors or augments perfusion of the coronary arteries.

As a result of this early experience, we feel that

Fig. 20. Lillehei's method of correction of aortic insufficiency due to prolapse or inversion of a cusp. (A) Prolapse of one cusp. (B) Secure (Ivalon reinforced) attachment of prolapsed cusp to an adjacent fellow thereby producing a conjoint cusp capable of supporting itself by virtue of its attachment to two-thirds of the aortic circumference. (C) Since subsequent fibrous infiltration of the Ivalon sponge will render the conjoint cusp significantly rigid, valve action thereafter will be essentially unicuspid in type.



A



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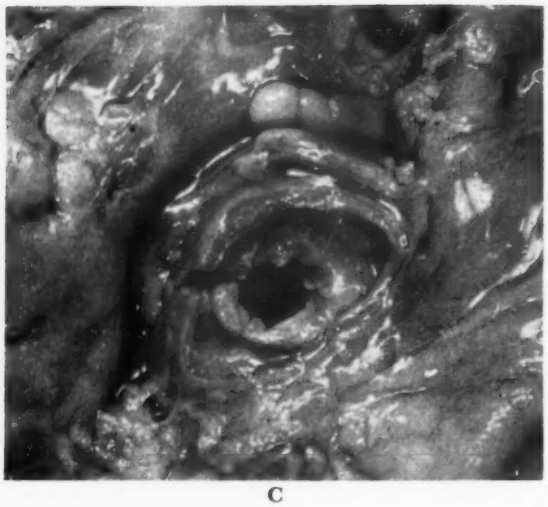
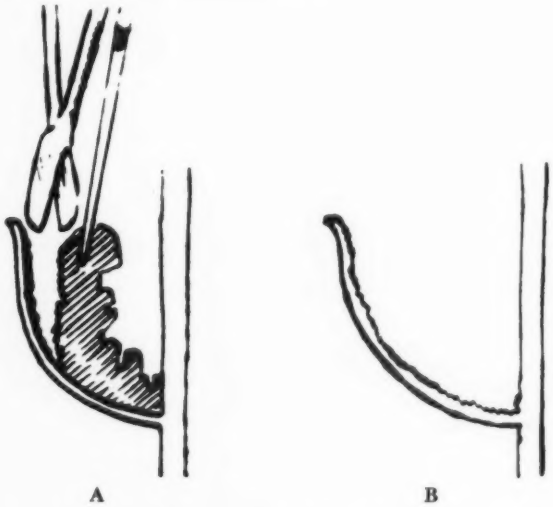


C

Fig. 21 (*left*). Valvular incompetence associated with lesions characteristic of aortic stenosis. (A) Preponderant aortic stenosis. Note calcification and thickening of the cusps which is largely restricted to the concave or "spongiosa" face of each cusp. Such a valve lends itself well to the "sculpturing" technic in which the structure is "thinned" until only the convex or "fibrosa" face remains. (From Bailey and Imbriglia;[11] Courtesy Charles C Thomas, Springfield, Ill., and Lea & Febiger, Philadelphia, Pa.) (B) Approximately equal amounts of the stenotic and regurgitant elements in an aortic valve whose cusps retain much of their normal cuplike configuration. (C) Extensive deformation of an aortic valve in which the cusps are thoroughly destroyed as entities. Probably only partial valvular excision and plastic repair is feasible in such a case.



A B

Fig. 22. (A) "Sculpturing" of an aortic valve cusp in which the scarred and calcified "spongiosa" layer is removed leaving the thinner flexible "fibrosa" layer. (B) A significant increment of "lengthening" of the thinned cusp is brought about by the sculpturing technic. This tends to diminish or overcome the regurgitant element in the valvular dysfunction.

bicuspid conversion or "bicuspidization" of the incompetent tricuspid aortic valve offers a satisfactory surgical solution in patients with "pure" aortic insufficiency in which the cusps remain flexible and of normal structure and configuration. Not only is a high order of valvular competence so provided, but no evidence of significant impedance to blood flow has been noted.

Aortic Insufficiency Due to Prolapse or Inversion of a Cusp

If the prolapsed cusp (Fig. 7) fortuitously should happen to be the noncoronary one, it would be simple enough to carry out the previ-

ously described procedure, converting the incompetent tricuspid valve into a competent bicuspid one. Whether or not an element of valvular stenosis would be produced, since presumably there would be no dilatation of the aortic root in such a case, is conjectural. Obviously such a procedure would not be feasible if the prolapsed cusp were a coronary-bearing one.

Actually, Lillehei[16] already has presented a reasonable and effective method by which bicuspid conversion can be brought about in such cases. The free margin of the prolapsed cusp is sutured securely using thin buffering strips of Ivalon sponge to one of the adjacent ones (Fig. 20). In case two cusps are prolapsed, they should be sutured together. In either instance, the resulting conjoint (double) cusp will be able to support itself adequately by virtue of its attachment to two-thirds of the aortic circumference. Infiltration of the Ivalon sponge with fibroblasts eventuates in stiffening by fibrosis, and this significantly reduces the flexibility and mobility of this conjoint cusp. Hence, the effective valve orifice will be reduced to approximately one-third of normal, and valvular function, thereafter, necessarily will be essentially unicuspid in type. However, this will suffice for the demands of a moderately active life.

Severe Aortic Insufficiency Combined with Aortic Stenosis

In cases of preponderant aortic stenosis, as mentioned previously, an element of incompetence frequently coexists (Fig. 21). Such insufficiency is not of major clinical significance, and often may be abolished by the effective "lengthening" of each cusp which attends definitive removal of its scarred and retracted concave "face" by the technic of valvular "sculpturing" which has been described elsewhere[10,11] (Fig. 22).

However, there are many cases in which severe aortic incompetence may occur in a valve which exhibits the same type of commissural obliteration and calcific encrustation which are so characteristic of aortic stenosis. In most of these patients, the "sculpturing" technic cannot overcome the valvular dysfunction since, even if significant flexibility could be restored to the cusps, the marked loss of tissue substance would preclude diastolic coaptation of the sculptured valve margins.

After much thought and consideration of certain tentative clinical attempts which have been detailed elsewhere,[6–8] the senior author finally became convinced that the solution to this problem lay in the attainment of the twin objectives of adequate orificial enlargement by subtotal excision of the rigid structure and reconstitution of the then grossly incompetent valve by a plastic procedure, employing some flexible contiguous (pedicled) structure. The full-thickness aortic wall appeared to offer us a suitable available tissue and seemed, moreover, to be exceptionally well adapted to withstand the incessant trauma and stress incident to the violent fluctuations in hydrodynamic pressures peculiar to the aortic valve level. The development by Fitch[17] of a watertight Ivalon-Teflon prosthetic material for aortic wall replacement encouraged us to accept the creation of a great defect of the aortic wall in the implementation of this concept.

Hence, after preliminary promising but inconclusive experimental studies upon mongrel dogs, when we were faced suddenly with this problem in the course of an open operation for calcific aortic stenosis, a technic was improvised for its accomplishment.

Case 10. On December 24, 1957, M. W. (#57-42077), a 43-year-old white male who had been suffering from chronic congestive heart failure for many months prior to operation (Fig. 23), including a serious exacerbation of this type during the course of his prolonged preoperative period of hospitalization (four weeks), was operated for predominant aortic stenosis at the Hahnemann Hospital. The systolic gradient across the aortic valve had been measured at 121 mm Hg. However, a grade 3 diastolic murmur and a low diastolic blood pressure (Fig. 24) suggested the coexistence of a significant element of aortic regurgitation. In the hope that extensive and effective sculpturing of the valve cusps might provide sufficient "lengthening" of their free margins to overcome much of the regurgitation, open aortic surgery was undertaken. At operation, both a strong systolic thrill and a very marked diastolic thrill were palpable over the root of the aorta. Total cardiopulmonary bypass with a bubble oxygenator was established. Elective cardiac arrest was induced with 70 cc of 3 per cent potassium citrate as advocated by Melrose[18] and Effler.[19]

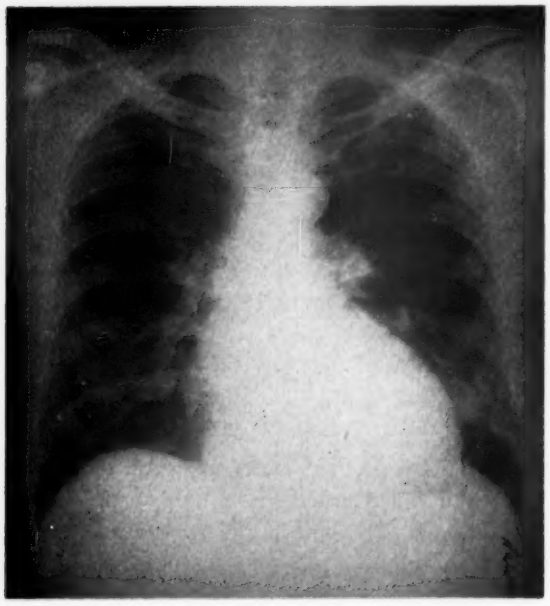


Fig. 23. Case 10. A 43-year-old white male with congestive heart failure due to aortic valvular disease.

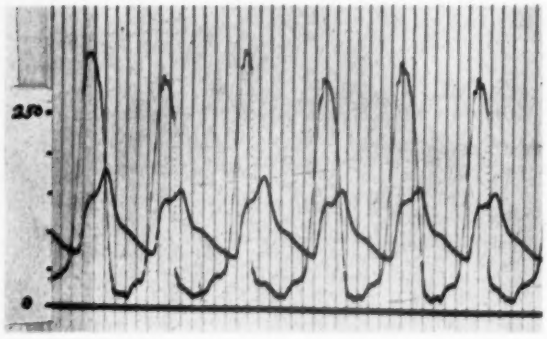


Fig. 24. Case 10. Note great systolic gradient (121 mm Hg) as shown in simultaneous superimposed tracings of left ventricular and aortic pressures.

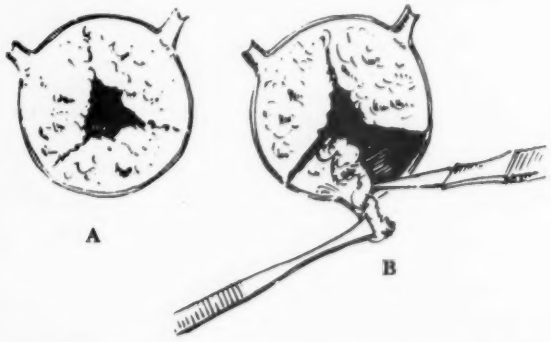


Fig. 25. Case 10. (A) Combined aortic stenosis and insufficiency in the presence of unsculpturable leaflets. (B) Excision of the noncoronary cusp.

To our chagrin each cusp was so infiltrated and replaced by calcific material that no effective sculpturing could be carried out. In desperation the original aortic incision was extended in such a way as to mobilize a tapering elliptical full thickness segment of aortic wall measuring 7 cm in length, taking up one-third of the aortic circumference at its midpoint, and pedicled at the base of the noncoronary cusp. This cusp then was excised, effectively overcoming the valvular stenosis (Fig. 25). The pedicled flap of aortic wall was buckled posteriorly and then was laid over the enlarged valve orifice, being tailored slightly in such a manner that it covered the entire opening without encroaching upon the coronary ostia. The tapering free extremity was attached to the anterior aortic wall at a level slightly above the obliterated remnant of the anterior (unopened) valve commissure, using through and through sutures of #2 braided silk and buffering patches of Ivalon sponge (Fig. 26). The aortic wall deficiency was

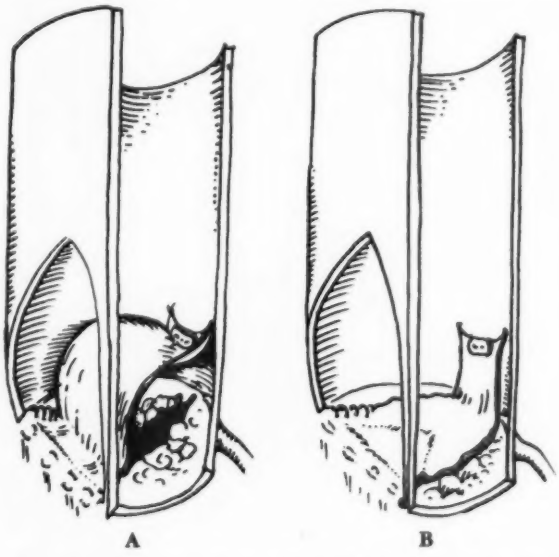


Fig. 26. Case 10. Preparation of flap valve from the full thickness of the aortic wall and its placement above the residual aortic valve orifice. (A) Systolic position. (B) Diastolic position, the valve aperture being tamponaded by the flap.

repaired using a tailored prosthetic patch consisting of a "sandwich" of Teflon mesh placed between two 1 cm thicknesses of Ivalon sponge which then was compressed to an over-all thickness of 3 mm. The aortic suture line also was buffered with 8 mm wide strips of uncompressed Ivalon sponge.

The period of total cardiopulmonary bypass was 62 minutes and the definitive (aortic) portion of the procedure required 51 minutes. The heart began to contract spontaneously within 5 minutes of re-establishment of perfusion of the coronary arteries and was aided by a period of assistance with rhythmic manual compression (to prevent overdistention of the left ventricle during its

feeble recovery period because of the presumed presence of some element of residual aortic valve incompetence). Soon a good beat was established and decannulation became possible. Palpation of the aortic root revealed a mild systolic thrill and an obvious shocklike vibration coincident with the onset of the diastolic phase presumably caused by sudden tamponade of the valve orifice by the flap. A much-reduced diastolic thrill was detectable over the aortic root.

Postoperatively, the patient did well physically but manifested a transient period of disorientation and psychosis which required his temporary transfer to an institution for psychiatric care. His diastolic blood pressure level has risen significantly (Fig. 27) and his over-all heart size has become reduced.

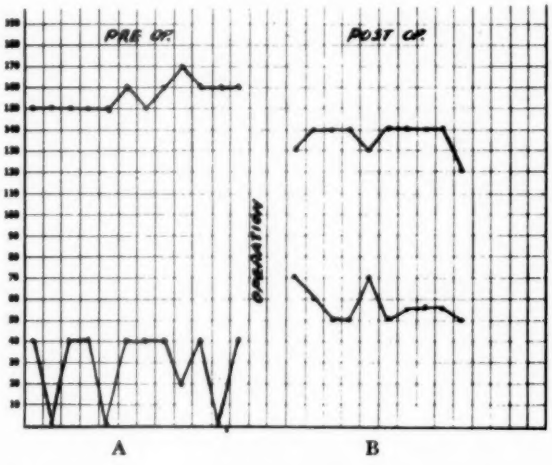


Fig. 27. Case 10. (A) Preoperative blood pressure chart. (B) Postoperative blood pressure chart.

A grade 4 systolic and a grade 2 basal diastolic murmur remain. A resounding aortic "2nd" sound is heard. Clinically he is much improved. All evidences of congestive heart failure have disappeared and he no longer is taking digitalis. However, it is felt that some aortic insufficiency persists, probably due to reflux of a portion of the flap below the valve level at both posterior "corners" of the triangular aortic aperture (Fig. 26).

COMMENT

It is believed that such a simple flap type valve does not provide an ideal type of control of aortic incompetence. Further, by its very mechanical presence in the line of the aortic flow, it must offer a hydrodynamically undesirable element of impedance to the circulatory pulse. However, it must be noted that a similar objection could be raised to the use of a Hufnagel ball valve, which clinically has proved its circulatory acceptability. Another disturbing consideration concerns itself with the eventual fate of such a flap graft under the continuous influence of the very severe mechanical trauma inherent in its type of action.

After considerable reflection based upon the initial considerable success of this effort, it was perceived that a significantly better tissue valve might be fabricated for application in this type of situation. Animal experimentation has been confirmatory of this advanced concept, and clinical trial awaits the appearance of a suitable case. By increasing the width of the elliptical arterial graft, by increasing the amount of "buckling" posteriorly, and by incising the

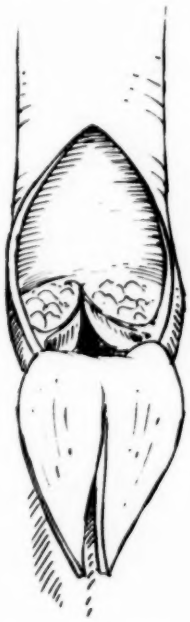


Fig. 28. Preparation of wide but "two-tailed" tapering flap from aortic wall. The noncoronary aortic cusp has been excised.

graft longitudinally (Fig. 28), two full-thickness strips of aortic wall can be provided which may be sutured to the entire length of the free margins of each of the remaining two (coronary bearing) cusps, thus greatly extending their "length" in a cephalic direction. The anterior extremities of the flaps may be individually affixed to the anterior aortic wall as in the previous technic, and the posterior "buckled" or "conjoint" extremity of the pedicled graft may be secured at as high a level as possible to the prosthetic patch which is used to replace the created aortic defect (Fig. 29). Thus a "bicuspid" conversion will have been accomplished, the two "elongated" cusps now becoming capable of coapting

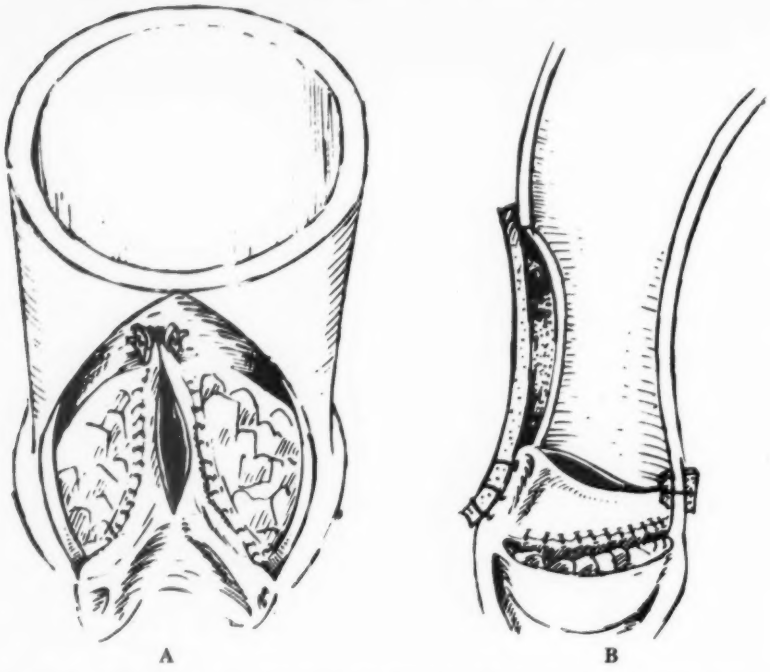


Fig. 29. (A) Top view showing attachment of lateral margins of "tails" to margins of remaining cusps thus effectively lengthening them. The anterior extremities of the "tails" are secured to the anterior aortic wall using Ivalon buffered sutures. (B) The conjoint posteriorly buckled (and pedicled) aortic wall graft is affixed as high as possible to the reparative prosthetic aortic patch, thus providing an effective bicuspid aortic valve.

completely along their flexible (grafted) margins. Moreover, such a valve would have the relatively gentle in-and-out motion of the natural aortic cusps and will not interpose a hydrodynamically undesirable mechanical obstacle directly into the course of the aortic current.

Summary

Feasible surgical technics have been devised and applied in the correction of the three most common types of acquired aortic regurgitation. The current rapid advances in the field of total cardiopulmonary and simple cardiac bypass (using the autogenous lung instead of an oxygenator) promise soon to reduce the entailed operative mortality to a reasonable level. Even at the present time, it seems worthwhile to apply these methods in individuals with severe aortic regurgitation who are in clinical difficulty. It is felt that definitive maintenance of coronary arterial perfusion by direct ostial cannulation during the course of the operation will permit maintenance of such myocardial vigor as to enable most of these very sick patients to survive operative intervention.

Addendum

The total number of patients operated on by a bicuspidizing technic at our clinic has now reached 40. Twelve have died (including those detailed herein). Three others have had a partial correction of the aortic incompetence. The remainder are greatly improved, many to the point of clinical cure.

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Studies in Mitral Stenosis

Cardiac Ventriculography in the Selection of Patients for Mitral Valve Surgery*

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In the past, selection of patients for mitral commissurotomy has depended for the most part on a critical analysis of the clinical features of the disease as well as a careful interpretation of the conventional x-ray studies and the electrocardiogram. Further helpful information has been obtained in some instances by the use of cardiac catheterization[1–3] and dye or isotope dilution data obtained during left heart catheterization.[4,5]

While this diagnostic approach has been successful on many occasions, problems frequently arise when the features of both mitral stenosis and regurgitation are combined, or when tricuspid regurgitation masquerades as mitral regurgitation in patients whose mitral valvular lesion is, in reality, pure mitral stenosis.[6]

The present report details our experience in the selection of patients for mitral valve surgery, employing a radiologic technic, cardiac ventriculography-left (direct transthoracic needle puncture opacification of the left ventricle).

Methods and Case Material

Forty-two patients with isolated rheumatic mitral valve disease were included in the present study. In each, direct opacification of the left ventricle was carried out preoperatively according to the technic of cardiac ventriculography described by Lehman, Musser, and Lykens.[7]

A high concentration radiopaque medium was injected rapidly via a subxiphoid approach into the left ventricle, with manometric monitoring of the ventricular puncture and continuous electrocardiographic control. Rapid serial filming during and following the injection of the dye into the ventricular cavity was employed.

The degree of regurgitation of the radiopaque material into the left atrium was then graded (1 + to 4 +) depending on the intensity of the left atrial opacification with due consideration of left atrial size. All interpretations were made by one of us (J. S. L.).

All of the cases were subsequently operated on and a palpatory appraisal of the mitral valve pathology made with estimation and grading of mitral valvular leak and stenosis. In 17, a mitral commissurotomy was performed, while 16 had a cross-polar plication (mitral annuloplasty) for correction of mitral regurgitation. Nine patients had a combined mitral commissurotomy and cross-polar plication.

Results

The correlation of the degree of regurgitant opacification of the left atrium with the findings at surgery is as follows:

(*a*) *No Opacification of the Left Atrium:* There were 9 cases in this group and all had a tight mitral stenosis at surgery without any regurgitation. A mitral commissurotomy was performed in all.

(*b*) *One Plus Opacification of the Left Atrium*

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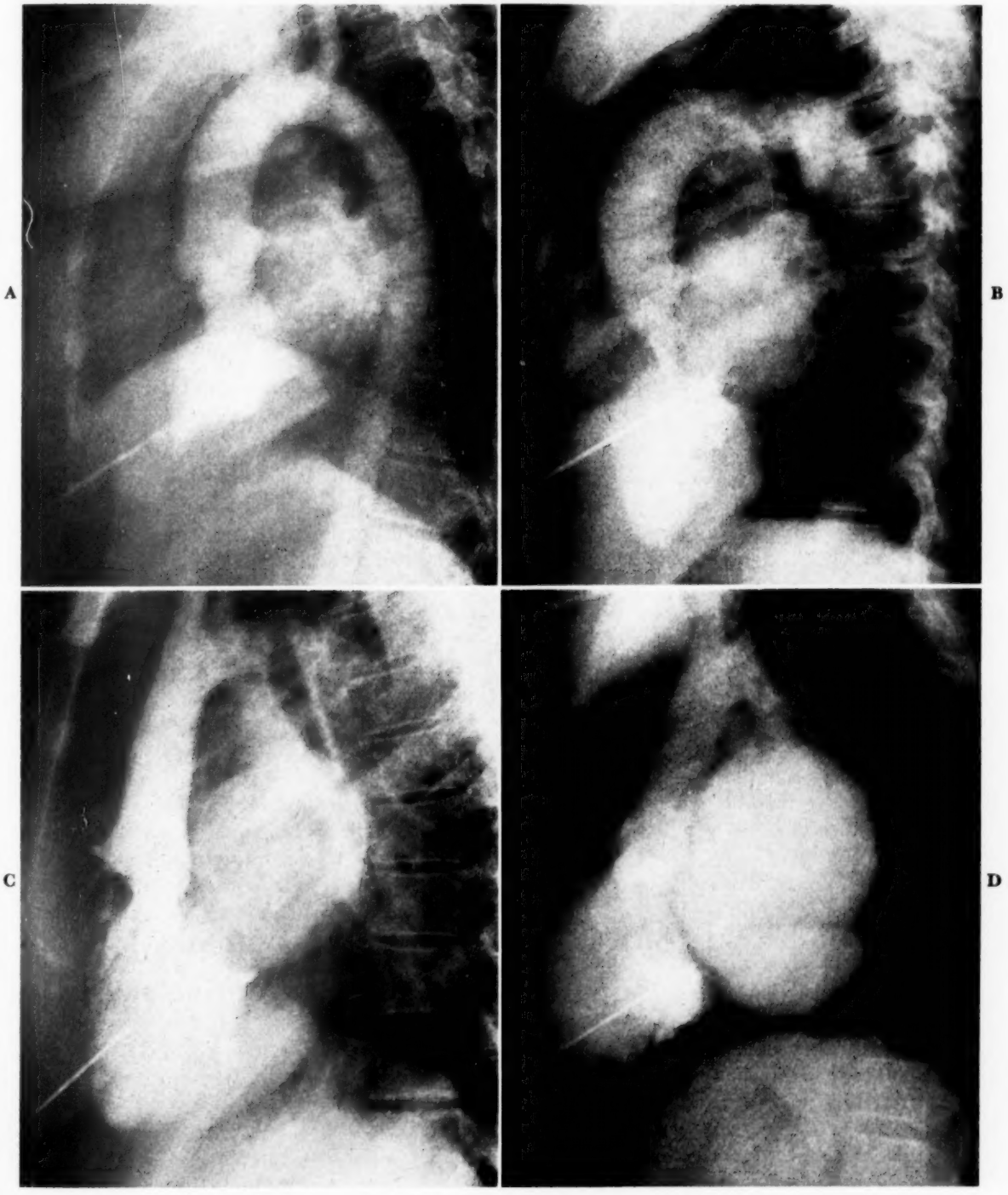

Fig. 1. Cardiac ventriculography-left. (A) 1+ opacification of left atrium; (B) 2+ opacification of left atrium; (C) 3+ opacification of left atrium; (D) 4+ opacification of left atrium. The grading of the degree of left atrial opacification is based on a range of 0 to 4+. Dynamic mitral regurgitation is always associated with greater than 1+ reflux opacification of the left atrium on cardiac ventriculography-left.

(*Fig. 1A*): There were five patients in this group. Only three had a minor degree of central regurgitation at surgery. All had a mitral commissurotomy performed.

(*c*) *Two Plus Opacification of the Left Atrium* (*Fig. 1B*): Twelve patients were in this category. All had dynamic leak at the posterior commissure. Four cases had a cross-polar plication performed alone; five had an anterior mitral commissurotomy and a posterior cross-polar plication, while three had a mitral commissurotomy alone.

(*d*) *Three Plus Opacification of the Left Atrium* (*Fig. 1C*): Thirteen patients were classified in this group. All had major regurgitation at the posterior commissure. Four had a combination of anterior commissurotomy and posterior cross-polar plication, while nine were operated on by the Nichols procedure (cross-polar plication) alone.

(*e*) *Four Plus Opacification of the Left Atrium* (*Fig. 1D*): There were three cases in this group. All had major mitral regurgitation posteriorly and were operated on by the cross-polar plication technic.

TABLE I

Correlation of Regurgitant Opacification of Left Atrium with Surgical Findings

Surgical opinion of anatomic lesion	Left atrial opacification				
	0	1+	2+	3+	4+
Pure mitral stenosis	9	2	—	—	—
Pure mitral regurgitation	—	—	4	9	3
Combined mitral stenosis and insufficiency	—	—	8	4	—
Major mitral stenosis, minor mitral insufficiency	—	3	—	—	—

Table I summarizes the ventriculographic interpretation of regurgitant opacification with the surgical opinion of the mitral valvular pathology.

There were 28 patients in whom an advanced and significant degree of mitral regurgitation was encountered at surgery. In each instance, it was limited to the posterior commissure. Twelve of these had some fusion of the anterior commissure as well.

In each of these 28, preoperative cardiac ventriculography demonstrated major reflux of dye into the left atrium, after instillation into the left ventricle. The intensity of the left atrial opacification was considered 2+ or greater on a grading basis of 0 to 4+.

In 11 others, a tight mitral stenosis was encountered at surgery, without regurgitation. Preoperative cardiac ventriculography demonstrated no left atrial opacification in nine and minimal (1+) reflux in two.

In three, the anterior and posterior commissures were found to be fused at surgery and a minor amount of central regurgitation was encountered. Preoperative cardiac ventriculography demonstrated 1+ opacification of the left atrium in each of these 3 cases.

Discussion

Cardiac ventriculography-left is a procedure designed to be of major assistance in the selection of cases for mitral commissurotomy. Its chief value has been in the identification of mitral regurgitation, for the presence of the latter lesion in dynamic form contraindicates the performance of an isolated mitral commissurotomy.

Our study demonstrates that direct transthoracic needle puncture opacification of the left ventricle has considerable reliability in the assessment of mitral valve leak, and our findings are in general conformity with those of the several published reports dealing with cardiac ventriculography in the diagnosis and quantitation of mitral insufficiency.[8,9] Its accuracy, confirmed by operative palpation of the mitral valve orifice, has been most impressive.

Every one of the 28 cases with proved dynamic mitral regurgitation had appreciable opacification of the left atrium on injection of the radiopaque medium into the left ventricle. There was no exception to this observation.

Findings in Pure Mitral Stenosis: Significant left atrial opacification (2+ or greater) was not observed in any patient in whom mitral stenosis was the major defect pathologically and hemodynamically.

In pure mitral stenosis, cardiac ventriculography was negative in nine while two showed minimal (1+) opacification of the left atrium. In the latter two patients, the surgeon reported no regurgitant jet, despite the preoperative roentgenographic report to the contrary.

It would appear that the method may be associated with false positives as illustrated by

these 2 cases. Whether these 2 cases represent instances where there was actually a slight functional leak of the mitral valve, detectable as minimal regurgitant opacification of the left atrium at the time of cardiac ventriculography, and not evident at surgery, or actually represent true false positives may well be a matter of some question. Arrhythmias may occur at the time of cardiac ventriculography or at surgery, and such arrhythmias, as they influence the stroke volume and the pressure within the left ventricle, may affect—for cardiac ventriculography on the one hand—the degree of atrial regurgitant opacification or—for surgery on the other hand—the strength and force of a minimal regurgitant jet leaking through the mitral valve.

At any rate, we are impressed by our observation that in no instance have we observed more than a very minimal opacification of the left atrium when the surgical findings described pure mitral stenosis. Conversely, a greater than 1+ opacification of the left atrium was confirmed by surgery as a significant dynamic mitral insufficiency in all such cases.

Clinical Diagnosis of Mitral Regurgitation: The clinical diagnosis of pure mitral regurgitation is not difficult to make. Cardiac auscultation reveals a loud apical systolic murmur. The murmur is usually blowing and radiates to the axilla. The mitral first sound is oftentimes obscured, and an opening snap is absent in about half of the cases.

In some cases, differentiation must be made between mitral regurgitation and tricuspid regurgitation. Such differentiation is not always easy on the basis of auscultation. In these cases, cardiac ventriculography-right (needle puncture opacification of the right ventricle) will reveal regurgitant opacification of the right atrium,[10] while cardiac ventriculography-left is negative for reflux into the left atrium. On the other hand, when marked anterior commissural fusion is present in addition to the posterior regurgitation, the auscultatory events related to mitral stenosis (sharp first sound, mid-late diastolic murmur with or without a thrill, opening snap) are also heard and clinical interpretation becomes difficult.

The electrocardiogram is of little help in the diagnosis of pure mitral regurgitation, for it demonstrates a pattern of left ventricular hypertrophy in only 30 per cent.[11] On the other hand, significant mitral valve leak may be present and the ECG may be normal, as it was in 50 per cent of this same series of 65 cases of pure mitral regurgitation. Right ventricular hypertrophy occurs in 15 per cent. The hemodynamic alterations responsible for this have been previously reported.[12]

The inadequacies of electrocardiograms are even more pronounced in combined mitral stenosis and regurgitation, where left ventricular hypertrophy is almost never encountered.

The difficulties in the interpretation of the conventional x-ray studies in mitral valve disease are related to problems in assessing ventricular hypertrophy.[13] The left atrium, in pure mitral regurgitation, is generally larger than in pure mitral stenosis, and left ventricular hypertrophy occasionally can be clearly demonstrated. However, the configuration of the heart may be identical in cases of mitral stenosis, mitral regurgitation, and combined lesions of the mitral valve.

Isolated mitral incompetence can also be demonstrated by injecting an indicator substance into the left atrium and left ventricle. A normal contour is obtained at the periphery when the dye or isotope is injected distally to the incompetent valve. An abnormal curve, characterized by small peak concentration, disproportionate prolongation of the disappearance slopes, and poor recirculation occurs if the indicator substance is injected proximal to the incompetent valve.[14]

Helpful information is also available in pure mitral regurgitation by analysis of the left heart catheterization data.[15] Left atrial pressure pulse curves may show a high C-V wave with a rapid descent in early diastole. The mean left atrial pressure is elevated and the end diastolic pressure of the left ventricle is higher than in patients with pure mitral stenosis.

All of these observations are seriously influenced by the pressure-volume relationships in the left atrium, as well as the size of that chamber. But more important is the fact that these special methods of determining mitral regurgitation lose their reliability in the presence of associated mitral stenosis. In this situation,

cardiac ventriculography has been more precise and accurate.

Complications of the Procedure: Cardiac ventriculography is not without some hazard. The chief complication to be feared is that of intramyocardial injection of the radiopaque material. Lehman and associates[7] have reported on the occurrence of this complication in an initial review of the technic. A further report covering experiences in the performance of over 200 cardiac ventriculographies and involving 2 fatalities is now in preparation by one of us (J. S. L.).

Indications for the Procedure: It would seem that the chief indications for the performance of cardiac ventriculography in the evaluation of mitral valvular disease would be those cases where uncertainty exists in regard to the exact amount of mitral regurgitation and stenosis. If significant opacification of the left atrium is demonstrated, then the performance of an isolated mitral commissurotomy is of little value. In our experience, the degree of mitral incompetence is little influenced by mobilization of the leaflets alone, unless an associated procedure is carried out to correct the regurgitation at the posterior commissure by a technic such as cross-polar plication.[16]

If only slight opacification of the left atrium is shown, then mitral commissurotomy is indicated for the leak may be central and of little dynamic significance, or it may represent the occasional false positive (1+) ventriculogram in a patient with pure mitral stenosis.

Summary and Conclusions

Cardiac ventriculography-left (direct transthoracic needle puncture opacification of the left ventricle) has been carried out successfully in 42 patients with isolated rheumatic mitral valve disease.

Twenty-eight patients with significant mitral regurgitation, proved at surgery, had greater than 1+ reflux opacification of the left atrium.

Fourteen patients with significant mitral stenosis, proved at surgery, were also studied. In nine, there was no reflux opacification of the left atrium while the remainder showed 1+ (slight) opacification of the left atrium.

There was no mortality or appreciable morbidity in this group of cases, although serious complications can occur if the test is not performed with care.

The chief indication for cardiac ventriculography-left appears to be those cases where uncertainty exists in regard to the exact amount of mitral regurgitation and stenosis.

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Pulmonary Function in Mitral Valve Disease

Hemodynamic and Ventilatory Studies*

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This report deals with the results of preoperative and postoperative venous cardiac catheterization and ventilatory function studies in patients with mitral valvular disease. Correlation of the hemodynamic and ventilatory patterns will be made.

In the past a tremendous amount of work has been done in this field by a number of clinical investigators from all over the world. To them credit must be given for our present knowledge of the pathophysiology of mitral stenosis and for a clear understanding of the pulmonary changes in this condition. We have investigated a large number of patients who underwent mitral commissurotomy,† and we believe that our results obtained are of sufficient clinical interest to warrant publication.

Material and Methods

CLASSIFICATION

Patients were classified under the following categories:

Group A: Patients with pure mitral stenosis whose functional capacity was nearly normal and mitral valve area was more than 1.5 cm².

Group B: Patients with pure or highly predominant mitral stenosis with severe functional incapacity, but without evidence of right heart failure. These patients were divided in two subgroups: Group B_1, in which the mitral surface was less than 1 cm²; Group B_2, in which the mitral surface ranged between 1.5 and 1 cm².

Group C: Patients with pure or predominant mitral stenosis and signs of combined heart failure.

Group D: Patients with mitral insufficiency, without evidence of failure (D_1) and patients with signs of combined cardiac decompensation (D_2).

HEMODYNAMIC STUDIES

Venous cardiac catheterization was performed in 150 patients. Of these, 65 were men and 85 females; their ages ranged between 15 and 54 years. Seventeen belonged to group A, 50 to group B_1, 19 to group B_2, 44 to group C, 8 to group D_1 and 12 to group D_2.

One hundred twenty-eight patients were submitted to mitral commissurotomy and five to plastic surgery of the valve for mitral regurgitation.

Central blood volume and mean circulation time were determined in 22 cases, using the dye (T 1824) dilution technic.

Ventilatory function was studied in 50 of the catheterized patients.

Cardiac catheterization was performed according to the method of Cournand and Ranges.[1] Formulae for calculations of the vascular and pulmonary resistances were the ones usually accepted. Intravascular pressures were recorded by means of a Sanborn electromanometer. The criteria proposed by Calazel[2] for pulmonary venous wedge pressure were fulfilled.

Cardiac index was calculated by the Fick method and in 22 cases by the dye dilution technic. Blood gas analysis was done in a Van Slyke apparatus and air gas analysis in a Haldane-Margaria apparatus.

Postcommissurotomy hemodynamic studies were carried out in 25 cases; 17 were recatheterized 30 to 40 days after surgery and 8 after a period of 6 months to 3.5 years.

Effort studies during catheterization were done in 10 instances: a steady effort of 40 watts/min for a 5 min period on a bicycle ergometer was required. Blood flow determinations and pressure recordings were obtained before and after the effort.

VENTILATORY STUDIES

Ventilatory studies were performed in 119 patients. Sixty-six were females and 53 were males; their ages ranged between 15 and 55 years. Commissurotomy

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† We are greatly indebted to Prof. A. M. Dogliotti for permitting us to study the very rich clinical material of the cardiac surgery center, Clinica Chirurgia Università di Torino, which he directs.

was performed in 99 cases and plastic surgery of the mitral valve in 4 patients. These subjects were so distributed: 12 in group A, 56 in group B, 38 in group C, 3 in group D_1, 10 in group D_2.

Static lung volumes were determined with a closed ventilated circuit Collins spirometer and residual volume with the helium dilution method.[3] The observed values were corrected to B.T.P.S.* Spirometric studies were performed with the patient seated. Ideal values were calculated with the formulae of Baldwin *et al.*[4] Resting minute ventilation (corrected to B.T.P.S.) was also determined by the spirographic method simultaneously with oxygen consumption. The ventilatory equivalent was then obtained: values of ventilation and of oxygen consumption were corrected to S.T.P.D.†

The mechanics of ventilation was studied by determining the maximum breathing capacity (M.B.C.), and the timed expiratory vital capacity (V.E.M.S). Ideal values were calculated according to Baldwin *et al.*[4] for M.B.C. and according to Graimprey[5] for V.E.M.S.

Alveolar ventilation was studied in 40 patients, with the method of Fenn[6] and Rossier.[7] Expired air was analyzed in the Haldane-Margaria apparatus. Oxygen and carbon dioxide contents of arterial blood were determined according to Van Slyke. Arterial blood pH was determined by a glass electrode pH meter (Metrom) at 37 °C.

Results

HEMODYNAMIC STUDIES

Pulmonary Blood Flow at Rest: Mean values for cardiac index (l/min/m^2) in each group of patients were as follows:

Group	
A	3.75 ± 0.44
B_1	2.40 ± 0.21
B_2	2.90 ± 0.30
C	2.14 ± 0.66
D_1	3.50 ± 0.62
D_2	2.20 ± 0.63

There was a statistically significant difference between cardiac index of group A and group B, of group B_1 and group B_2, as well as between group D_1 and group D_2 ($P < 0.01$). No statistically significant difference could be found between groups B and C.

Pulmonary Artery Pressure: The following mean values for pulmonary artery systolic and diastolic pressures in mm Hg were calculated:

Group	*Systolic*	*Diastolic*
A	35 ± 7.1	17 ± 7
B_1	68 ± 21.5	33 ± 10
B_2	57 ± 14.1	30 ± 10
C	96 ± 25.4	45 ± 14
D_1	45 ± 6	24 ± 13
D_2	64 ± 21	32 ± 16

Statistically significant differences for systolic pressures were found between group A and group B_2, between group B_1 and group B_2 and between group C and group B_1 ($P < 0.01$).

Pulmonary "Capillary" Pressures: Mean values for mean pulmonary "capillary" pressures in mm Hg were as follows:

Group	
A	15.5 ± 5
B_1	29 ± 6.7
B_2	27 ± 6
C	34 ± 5.8
D_1	20 ± 5
D_2	28 ± 6.2

A statistically significant difference ($P < 0.01$) was found between groups A and B_2 as well as between group B_1 and group C.

The difference between group B_1 and group B_2 was not statistically significant.

Effort Studies: Cardiac index on effort rose in each instance (Table I). In the two patients with good functional capacity (group A), for each 100 cc increase of oxygen consumption the cardiac index rose 1,300 and 900 cc respectively. In the remaining seven patients with great functional incapacity, cardiac index augmentation, for each 100 cc increase of oxygen consumption, ranged between 105 and 372 cc/min.

A definite increase of pulmonary venous wedge pressure and pulmonary artery pressure was observed in one of the two patients of group A and in each case of groups B_1 and C.

Pulmonary Blood Volume and Mean Circulation Time: Mean value for central blood volume was 606 ± 120 cc/m^2; the values varied between 970 cc/m^2 in a patient subjected to mitral commissurotomy, and 410 cc/m^2 in a patient of group C. The mean value of mean circulation time was 15 sec ± 3.2.

Postcommissurotomy Hemodynamic Studies: After mitral commissurotomy cardiac index rose significantly in 13 out of the 20 patients in which it was low preoperatively, reaching normal

* B.T.P.S. = Body temperature, ambient pressure and H_2O saturation.

† S.T.P.D. = Standard temperature (0 °C) and pressure (760 mm Hg), dry.

TABLE I

Hemodynamic Findings Before and After Effort in Patients with Mitral Stenosis

Case Number	Age (Years)	Sex	Functional Class	Vo_2/m^2	A.V. (vol %)	C.I. (l/min/m^2)	P.A.P. (mm Hg)	P.C.P. (mm Hg)
1	27	♀	A	145	4.82	2.73	40/20	18
				216	6.40	3.37	42/22	20
2	32	♀	A	138	4.00	3.40	25/12	10
				256	5.09	5.00	35/15	18
31	19	♂	B_1	137	6.40	2.15	40/20	25
				240	9.00	2.70	70/35	35
32	28	♀	B_1	110	5.10	2.15	48/30	28
				192	7.88	2.44	60/40	35
33	32	♀	B_1	124	5.95	2.09	40/25	20
				190	8.20	2.32	60/40	30
34	27	♂	B_1	135	5.55	2.37	65/35	32
							90/50	42
35	35	♀	B_1	125	5.88	2.14	50/30	24
				177	7.70	2.30	65/35	35
98	39	♂	C	129	5.64	2.46	70/42	30
				207	7.60	2.58	100/58	55
99	32	♀	C	140	7.07	1.90	110/50	50
				246	9.80	2.40	140/65	70

Vo_2/m^2 = Oxygen consumption per square meter of body surface; A.V. = arteriovenous difference (vol. %); C.I. = cardiac index (l/min/m^2); P.A.P. = pulmonary artery pressure (mm Hg); P.C.P. = pulmonary "capillary" mean pressure (mm Hg).

values in 10 cases (Table II). No changes were observed in the other subjects.

Pulmonary artery pressures decreased in 23 patients. The postcommissurotomy drop of pulmonary systolic pressure ranged between 10 and 90 mm Hg. Pulmonary "capillary" pressure fell in 22 cases, but normalization was achieved in only 9 patients.

VENTILATORY STUDIES

Vital Capacity (V.C.): Mean values for V.C. expressed in percentage of the ideal value according to Baldwin[4] were the following:

Group	*%*
A	111 ± 40
B	96 ± 32
C	82 ± 19
D	97 ± 21
D_2	75 ± 18

A statistically significant difference ($P < 0.01$) was found between the values of group A and those of group B; the difference between groups B and C was also statistically significant ($P < 0.01$).

Residual Lung Volume (R.V.) and Total Lung Capacity (T.L.C.): These parameters were determined in 32 patients of group B, in 18 of group C, and in 8 patients of group D_2. The mean values and standard deviations were the following:

Functional Residual Capacity		*Total Lung Capacity*	
Group		*Group*	
B	3,290 cc ± 900	B	5,350 cc ± 1,135
C	2,900 cc ± 720	C	4,460 cc ± 1,280
D_2	2,580 cc ± 800	D_2	4,111 cc ± 700

Residual Volume		*Residual Volume/Total Lung Capacity Ratio*	
Group		*Group*	
B	2.090 cc ± 700	B	38 ± 7
C	1.890 cc ± 565	C	42 ± 8
D_2	1.697 cc ± 500	D_2	41 ± 9

In each group the value of the ratio between residual volume and total lung capacity was definitely increased. No statistically significant difference could be found between mean values of total lung capacity, residual volume, functional residual capacity and R.V./T.L.C. ratio in the various groups of patients.

TABLE II

Hemodynamic Changes Induced by Mitral Commissurotomy

Case Number	Age (Years)	Sex	Functional class	Rhythm	C.I. (l/min/m^2)	P.A.P. (mm Hg)	P.C.P. (mm Hg)	Time after surgery—Results
18	35	♂	B_1	S	3.72	68/24	25	16 months—Fair
				A.F.	3.05	45/22	14	
19	34	♀	B_1	S	2.73	80/42	35	11 months–Good
				S	2.38	45/28	18	
22	37	♀	B_1	S	2.07	135/55	38	3 years–Good
				A.F.	2.50	45/28	15	
27	33	♂	B_1	S	3.60	70/30	24	30 days–Good
				S	3.20	40/20	11	
28	31	♀	B_1	S	2.44	48/30	28	30 days–Good
				S	2.65	25/10	12	
29	27	♀	B_1	S	2.03	55/30	25	40 days–Good
				S	2.95	45/16	9	
30	34	♀	B_1	A.F.	3.54	58/25	25	40 days–Fair
				A.F.	3.61	50/20	20	
38	29	♂	B_1	S	2.30	100/60	32	7 months–Good
				S	3.40	45/30	16	
54	27	♂	B_1	A.F.	2.40	45/18	20	19 months–Fair
				A.F.	2.38	50/30	15	
61	45	♂	B_1	S	2.80	80/25	25	40 days–Fair
				S	3.50	60/30	25	
68	35	♂	B_2	A.F.	2.02	85/54	40	3 years–Good
				A.F.	2.17	55/25	18	
71	37	♀	B_2	S	1.89	60/25	22	30 days–Good
				S	2.65	35/10	12	
72	44	♀	B_2	S	2.75	60/28	30	30 days–Good
				S	2.89	25/8	6	
73	31	♀	B_2	S	3.28	80/50	22	40 days–Good
				S	4.08	25/10	10	
74	29	♀	B_2	S	2.70	60/40	25	40 days–Good
				S	2.36	45/20	12	
75	30	♀	B_2	S	2.46	50/28	30	30 days–Fair
				S	3.23	42/20	20	
76	39	♀	B_2	S	3.66	50/20	26	30 days–Good
				S	4.31	48/20	18	
78	43	♂	B_2	S	2.20	80/40	37	3.5 years–Good
				A.F.	2.70	40/18	15	
93	43	♀	C	A.F.	1.62	60/30	29	40 days–Good
				A.F.	2.26	38/12	12	
94	29	♀	C	S	1.74	80/42	33	30 days–Good
				S	3.17	50/20	15	
95	27	♂	C	S	1.62	110/55	35	40 days–Fair
				S	2.06	80/35	25	
96	15	♀	C	S	1.47	120/55	36	40 days–Good
				S	2.52	80/40	24	
97	37	♂	C	S	1.32	140/40	36	32 days–Poor
				S	2.62	130/45	30	
102	46	♂	B_1	A.F.	1.56	90/40	35	3.5 years–Good
				A.F.	3.60	42/20	15	
105	33	♂	C	S	1.76	95/40	38	3.5 years–Good
				A.F.	2.70	30/15	8	
131	22	♂	D_1	A.F.	3.76	50/30	36	40 days–Poor
				A.F.	3.50	35/12	18	

Symbols as in the other tables.

TABLE III

Alveolar Ventilation in Mitral Disease

Case number	Age (Years)	Sex	V/m² (ml)	V_A/m² (ml)	D (ml)	D / T.V. × 100	V_{CO_2} (ml/m²)	pH	P_{aCO_2} (mm Hg)
	Group A								
9	41	♀	5,180	3,320	152	36	154	7.37	40
163	35	♂	9,400	7,950	105	15	230	7.51	25
164	39	♀	6,000	4,220	178	29	157	7.43	32
165	30	♀	8,340	5,230	161	37	212	7.45	35
166	35	♀	4,400	2,930	125	33	125	7.36	37
	Group B								35
64	36	♀	4,460	2,800	185	37	114	7.42	31
81	36	♂	6,250	4,660	254	25	171	7.45	39
162	44	♂	6,280	4,540	180	27	205	7.41	33
167	42	♂	5,560	3,900	165	29	149	7.35	40
168	27	♀	3,570	2,440	100	31	113	7.46	40
169	28	♂	7,600	3,830	362	48	177	7.43	35
170	36	♂	6,700	4,400	178	35	178	7.43	33
171	37	♀	4,710	3,660	91	22	138	7.45	35
172	49	♀	3,920	2,490	165	36	94	7.36	35
173	15	♀	7,280	3,670	237	49	149	7.40	39
174	48	♀	4,410	2,450	220	44	110	7.42	40
175	50	♀	4,810	2,100	300	56	97	7.39	30
176	44	♀	5,400	4,260	142	21	148	7.46	36
177	42	♂	5,780	3,660	185	36	153	7.43	31
178	37	♀	7,450	5,160	186	35	185	7.43	37
179	34	♂	6,330	3,325	207	47	142	7.39	34
180	32	♂	5,050	3,750	150	25	148	7.40	35
181	45	♂	5,090	3,280	175	35	133	7.40	34
182	31	♂	6,350	4,140	208	34	164	7.43	

V = minute ventilation per square meter body surface; V_A = alveolar ventilation per square meter body surface; D = dead space; T.V. = tidal volume; P_{aCO_2} = arterial CO_2 partial pressure.

Maximum Breathing Capacity (M.B.C.): The mean values of M.B.C. in percentage of the ideal values were as follows:

Group	%
A	77.9 ± 24.3
B	66.5 ± 17.5
C	51 ± 16
D_1	Not calculated
D_2	46 ± 10

A statistically significant difference was found between group B and group C ($P < 0.01$).

Timed Expiratory Vital Capacity (V.E.M.S.): The following figures are the mean values for each group, expressed in percentage of the ideal values.

Group	%
A	118 ± 26
B	92 ± 18
C	70 ± 18
D_1	94 ± 18
D_2	68 ± 18

The difference between group B and group C was statistically significant ($P < 0.01$).

Minute Resting Ventilation (V), Oxygen Consumption (V_{O_2}) and the Ventilatory Equivalent for O_2 (V.E.): The following values were obtained:

TABLE IV
Spirographic Findings Before and After Commissurotomy

Case Number	Age (Years)	Sex	V.C. cc (%)	V.E.M.S. (cc)	V.E.M.S. % / V.C.	M.B.C. l/min (%)	V.E.	Time after surgery (months)
18	35	♂	3,930 (95)	2,950	75	137 (112)	22	16
			3,380 (81)	2,180	64	88.2 (73)	45	
19	34	♀	2,630 (91)	2,070	78	49.3 (45)	22	11
			2,410 (82)	1,810	75	48.1 (51)	41	
31	19	♂	3,480 (90)	3,040	87	69.6 (66)	60	1
			2,940 (76)	2,500	85	69.5 (66)	40	
34	27	♂	4,400 (110)	3,580	81	86.9 (82)	42	3
			3,100 (79)	2,500	80	65 3 (62)	95	
38	29	♂	3,880 (100)	3,160	81	120 (111)	74	7
			3,610 (92)	2,730	75	101 (92)	48	
54	27	♂	5,950 (133)	3,600	60	126 (93)		19
			4,780 (107)	3,280	68	87.2 (66)	35	
68	36	♂	3,860 (94)	2,940	76	159 (141)	32	36
			3,080 (77)	2,180	71	68 (58)	57	
69	33	♀	3,770 (126)	3,115	82	54.6 (63)	20	23
			3,480 (113)	2,820	81	65.3 (73)	26	
89	20	♂	2,950 (69)	2,725	92	80 (86)	42	21
			2,950 (70)	2,240	76	83.8 (73)	35	
112	29	♀	2,130 (74)	1,640	77	34.2 (46)	43	3
			2,170 (75)	1,750	80	43 (58)	34	
188	48	♂	3,330 (94)	2,240	67	56.7 (64)	27	1
			2,480 (68)	1,750	71	35 (60)	46	

V.C. = Vital capacity (in parentheses % of predicted values); V.E.M.S. = Timed expiratory vital capacity; M.B.C. = Maximum breathing capacity (in parentheses per cent of predicted values); V.E. = Ventilatory equivalent for O_2.

Group	V (l/min/m²)	V_{O_2}(cc/min/m²)	V.E.
A	5.3 ± 0.9	125 ± 10	35.1 ± 9
B	5.7 ± 1.3	129 ± 29	36.7 ± 11
C	5.8 ± 1.2	132 ± 27	37.3 ± 10
D_1	4.85	132 ± 14	33.3 ± 12
D_2	6.02 ± 1.6	126 ± 24	41.7 ± 9

Alveolar Ventilation (V_A): This was found to be constantly increased as well as the functional dead space. However, the values were rather widely dispersed even for patients of the same group. Furthermore, as shown in Table III, blood pH was constantly increased, simultaneously with a fall of CO_2 partial pressure.

Postcommissurotomy ventilatory studies were carried out in 11 patients. Pre- and postoperative results are given in Table IV.

HEMODYNAMIC PATTERN IN MITRAL STENOSIS

Curtailment of blood flow, one of the characteristic features of mitral stenosis, was confirmed by our studies. Furthermore, our findings indicate that the diminution of cardiac index parallels closely the anatomic degree of narrowing of the mitral orifice. Therefore it would appear that mechanical mitral block per se, when severe, represents the main factor producing the fall of peripheral blood flow. However, as will be discussed more extensively in the following paragraphs, some degree of left ventricular failure, at times clinically latent, can also contribute to the reduction of the cardiac output.

The inadequacy of peripheral blood flow in mitral disease is demonstrated also by the marked increase of the A-V difference occurring on effort in those cases with severe functional impairment. In fact, in patients with tight mitral block the cardiac output increases on effort much less than one would expect for a given O_2 consumption.

An increase of pulmonary wedge pressure, a fairly good approximation on left atrial pressure, is a

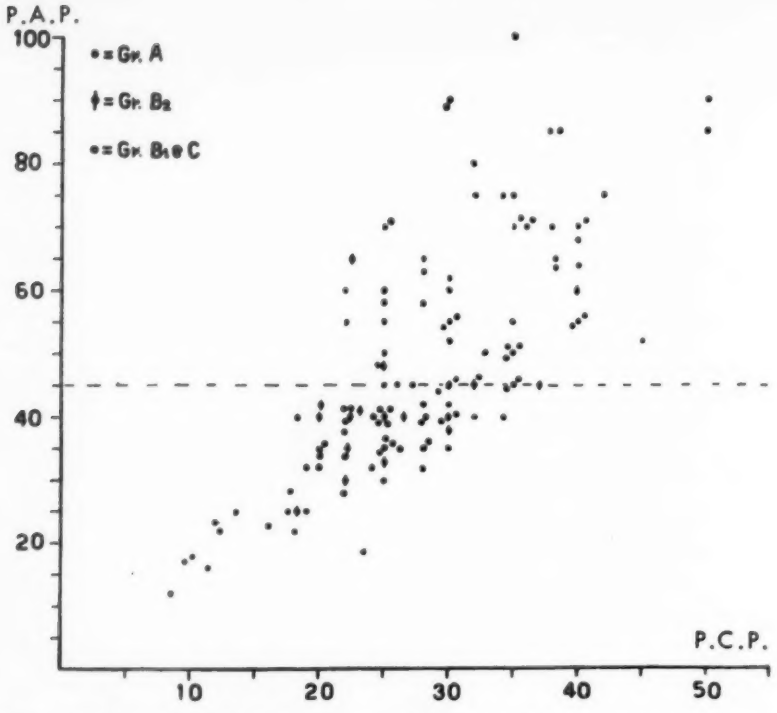

Fig. 1. There is a positive linear correlation (r = 0.69) between pulmonary mean "capillary" pressure (P.C.P. in mm Hg) and pulmonary artery systolic pressure (P.A.P. in mm Hg) when the latter does not exceed 45 mm Hg. Above this arbitrary level, correlation between the two parameters is lacking.

well known fact in mitral stenosis, at rest and/or on effort. We did observe a sharp and significant increase of pulmonary wedge pressure in patients with pure stenosis when the mitral surface was less than 1.5 cm². However, a decrease of the mitral valve surface under this anatomic limit did not seem to be responsible, on the whole, for further elevation of pulmonary "capillary" pressure.

This might be due, as postulated by earlier workers,[8] to the "protective" action of the increased pulmonary arteriolar resistance on the capillary vascular bed. Furthermore, it must be considered that pulmonary wedge pressure is a function not only of the mitral block, but also of blood flow through the mitral orifice and, as previously stated, of the left myocardial fitness. In fact, some evidence suggests that even in pure tight mitral stenosis some degree of left ventricular failure may be present, which cannot be detected by the usual clinical means.[9]

This hypothesis was verified in our laboratory[10] by studying the hemodynamic action of lanatoside C given intravenously to patients with pure isolated mitral stenosis and no clinical or laboratory evidence of rheumatic activity. Some of these patients, under the action of the drug, exhibited a marked fall of the pulmonary "capillary" pressure with a simultaneous increase of cardiac output, independent of any change of the heart rate and of right atrial and ventricular diastolic filling pressure. Similar observations have been reported by others;[11] the possibility of left ventricular failure as a cause of symptoms in some cases of pure mitral stenosis is also suggested by left heart catheterization studies.[12]

Pulmonary artery pressures paralleled, within certain limits, changes of pulmonary "capillary" pressure. However, we have observed that only pulmonary artery systolic pressures not exceeding 45 mm Hg were linearly correlated with pulmonary wedge pressure (Fig. 1). This finding suggests that minor degrees of pulmonary hypertension in mitral stenosis represent mainly a passive phenomenon re-

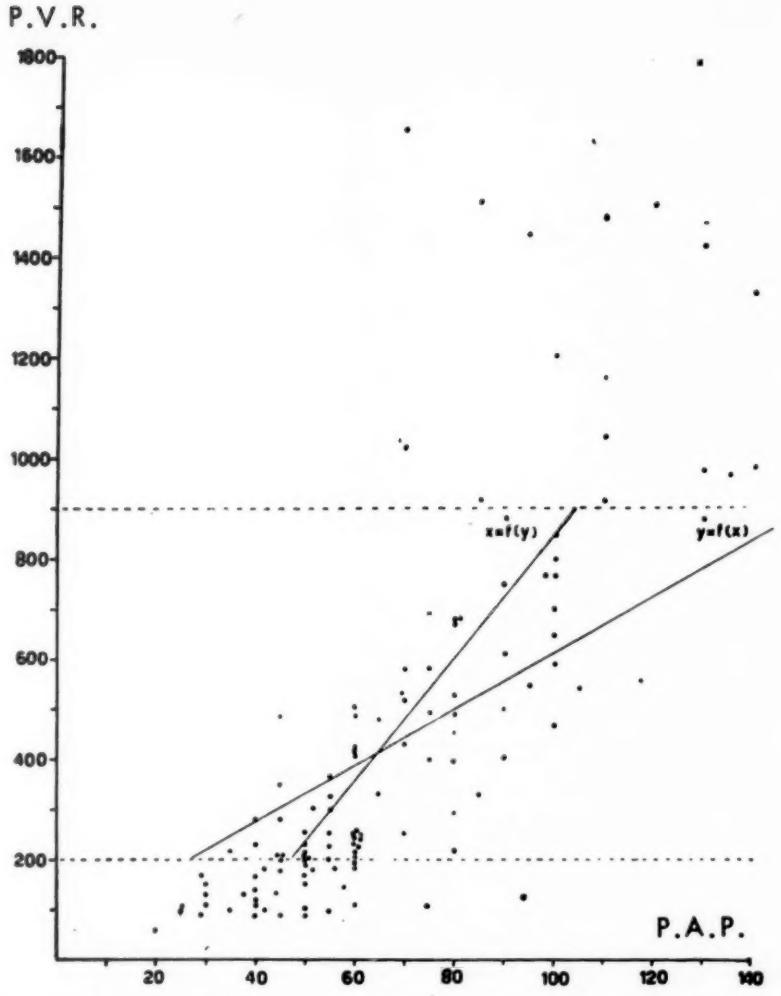

Fig. 2. A positive linear correlation (r = 0.67) exists between pulmonary artery systolic pressure (P.A.P., mm Hg) and pulmonary vascular resistances (P.V.R., dynes sec cm^{-5}) within an arbitrary range of P.V.R. (from 200 to 900 dynes sec cm^{-5}) (see text). A similar correlation was found between pulmonary artery diastolic pressure and P.V.R. (r = 0.61).

sulting from backward transmission of left atrial and pulmonary venous hypertension. No correlation between pulmonary "capillary" pressure and pulmonary systolic pressure could be observed in our series of patients when the latter exceeded 45 mm Hg.

Evidently other factors besides the mitral block are operating in producing the pulmonary hypertensive state of mitral stenosis. It is well known that these factors are represented by the pulmonary vascular resistances (P.V.R.). In fact we found that for values between 200 and 900 dynes sec cm^{-5} a statistically significant correlation was present between pulmonary vascular resistances and pulmonary systolic or diastolic pressures (Fig. 2). Similar observations have been previously made by Fowler.[13,14] The above correlation was much poorer when the level of 900 dynes sec cm^{-5} was reached. A detailed analysis of the cases in which P.V.R. were more than 900 dynes sec cm^{-5} showed that the disproportionate increase of the pulmonary vascular resistances was chiefly due to an extremely low cardiac index. All these patients were fibrillating and exhibited severe signs of cardiac failure. Lack of correlation between P.V.R. and pulmonary artery pressures when the former are less than 200 dynes

sec cm^{-5} confirms that the increased P.V.R. play a minor role in cases with moderate pulmonary hypertension.

The pulmonary hemodynamics at rest of combined mitral stenosis and insufficiency, with predominance of the latter and in the presence of functional incapacity, were very similar to those outlined above for pure mitral stenosis. Pulmonary systolic pressures up to 105 mm Hg were found in some of the cases with predominant mitral regurgitation; in these patients the clinical, radiologic and electrocardiographic picture was almost indistinguishable from the one of tight mitral block. A logical explanation for this situation has been given by Dexter,[15] who has stressed the importance of the increased blood flow through the incompetent mitral orifice in making functionally severe an otherwise anatomically mild mitral narrowing.

In far advanced cases the importance of anatomic *vascular changes of the pulmonary bed* as a cause of pulmonary hypertension in mitral stenosis is quite obvious and sufficiently demonstrated by the angiopneumographic and biopsy studies. However, there is increasing convincing evidence that *functional factors* can also play an important role. A series of pharmacodynamic studies on men and animals have shown that a fall of pulmonary artery pressure can be produced by a number of ganglioplegic and sympathicolytic drugs.[16–18]

In our laboratory[19] it has been possible to demonstrate that reserpine given intravenously to patients with mitral stenosis produces a marked drop of pulmonary artery pressure, independent of any changes of cardiac output, heart rate, systemic blood pressure and pulmonary venous wedge pressure. These results have been confirmed by Halmagyi.[20]

The hemodynamic pattern which has been outlined above seems to be rather characteristic of mitral stenosis and shows a fair correlation with the degree of anatomic and functional impairment. On the contrary, as observed also by other workers,[21–25] ventilatory function studies did not yield similarly consistent results.

VENTILATORY PATTERNS IN MITRAL STENOSIS

Static lung volumes were markedly impaired only in cases with tight mitral stenosis and serious functional incapacity. These patients showed a definite increase of residual volume (R.V.) with a fairly proportional diminution of vital capacity (V.C.). Total lung capacity (T.L.C.) therefore remained nearly normal, with a resultant increase of the ratio R.V./T.L.C. In decompensated patients there was a further expansion of R.V., but due to a more marked decrease of V.C., the T.L.C. was slightly reduced.

Among the *dynamic tests of ventilation*, maximum breathing capacity (M.B.C.) was the one which more closely reflected the clinical situation. However, here again, rather widespread values were observed in patients of the same group.

The timed expiratory vital capacity (V.E.M.S.), an index of bronchial patency, was significantly altered only in decompensated patients. In the other patients with tight mitral stenosis, changes in this test were much less pronounced than one would have expected from the degree of dyspnea. Bronchial obstruction, as a contributory cause of respiratory derangement, does not seem to play an important role in the absence of congestive heart failure.

Factors Causing Ventilatory Changes: Many factors operate to produce these ventilatory changes. The importance of the impairment of the elastic properties of the lungs is well known.[21,26–29] Vascular engorgement is one of the factors frequently stressed as a cause of lung rigidity in mitral stenosis. However, using the dye dilution technic, we were unable to demonstrate any increase of intrapulmonary blood volume in our patients. These findings are in agreement with those of Rappaport and co-workers,[30] and have been explained on the basis of the positive correlation existing between intrapulmonary blood volume and the low cardiac index in mitral stenosis.

Previous experimental work[31,32] has suggested that pulmonary hypertension per se can represent an important factor of lung rigidity. This hypothesis could not be confirmed by our findings. In fact, in 50 of our patients in whom hemodynamic and ventilatory studies were carried out simultaneously, the correlation

between the level of pulmonary blood pressures and static lung volumes was found to be rather poor. It is therefore apparent that other factors, such as the general condition, pulmonary parenchymal lesions, hepatomegaly, ascites, etc., can make an important contribution to the ventilatory impairment of mitral stenosis. The resultant increased work of breathing is probably due to the combined influence of all the above mentioned factors.

Alveolar Ventilation: Previous studies on alveolar ventilation have shown that in mitral stenosis the functional dead space is consistently increased, due to an increase of venous admixture and to a diminution of the oxygen diffusing capacity.[22,23,33–36] Results obtained in 40 of our patients confirm, on the whole, these findings. In mitral stenosis alveolar ventilation is increased with a simultaneous expansion of the functional dead space, substantially indicating the presence of a perfusion defect in this condition.

Diagnostic Value of Ventilatory Changes: It is apparent from our results that ventilatory function studies in mitral stenosis have at present a rather limited diagnostic value. This must be due to the interference of many other factors (pulmonary fibrosis and emphysema, pleural adhesions, pulmonary infarctions, emotional factors, etc.) superimposed on the cardiac condition, which may not be easily recognizable clinically. It is our experience, however, that a normal ventilatory pattern represents a most favorable prognostic index in the preoperative evaluation of a patient with mitral stenosis.

Hemodynamic and Ventilatory Changes Following Commissurotomy: The outstanding hemodynamic findings following mitral commissurotomy was the marked drop of pulmonary artery and pulmonary wedge pressures as observed in all but three of our patients. Although the fall of pulmonary pressures was usually conspicuous, normal values were seldom reached. On the whole, the hemodynamic behavior following mitral commissurotomy was very similar to the one present preoperatively in subjects with moderate degree of mitral narrowing. Changes induced by commissurotomy occurred very early following surgery. In 15 of the 17 patients recatheterized 30 to 40 days after the operation the pulmonary hemodynamics had already undergone profound modifications.

The hemodynamic changes following commissurotomy in most cases seemed to follow closely the clinical improvement. On the contrary, postcommissurotomy ventilatory studies gave quite variable and at times disappointing results, even in patients clinically ameliorated and examined up to two years after surgery. Actually, deterioration of spirographic tests was rather common in spite of objective and subjective improvement of the cardiac situation. These observations in a small number of patients do not allow any general conclusion. Only the study of a larger series of patients will assess their real significance.

Summary

Hemodynamic and ventilatory studies were carried out in a large series of patients who underwent mitral surgery for mitral stenosis or insufficiency.

A diminution of cardiac index was found, which paralleled the narrowing of the mitral orifice. However, left ventricular failure seemed to be operative in some of the cases, even in the presence of pure, tight mitral stenosis. This hypothesis was also suggested by the observation that pulmonary artery and venous wedge pressures were significantly higher in patients with combined heart failure, independently of the size of the mitral orifice.

A positive linear correlation was found between pulmonary artery pressures and pulmonary vascular resistances, when the latter were more than 200 and less than 900 dynes sec cm^{-5}.

No significant increase of pulmonary blood volume could be found in patients with mitral stenosis.

Lack of correlation was found between ventilatory and hemodynamic findings studied simultaneously in 50 patients.

Vital capacity was significantly impaired only in decompensated patients. Residual volume was increased in every case of mitral disease. Ventilatory dynamics were also altered in every instance, particularly when congestive heart failure was present.

Functional dead space was consistently increased, in spite of an increased alveolar ven-

tilation. These findings confirm that in mitral stenosis the ventilatory perfusion ratio is consistently impaired. Results of postcommissurotomy ventilatory studies were quite variable in spite of good clinical results.

In 26 patients the hemodynamic behavior was studied before and at varying intervals (30 days to 3.5 years) after mitral commissurotomy. The hemodynamic findings in patients who underwent a successful commissurotomy are similar to those observed in subjects with anatomically and functionally mild mitral stenosis.

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Central Blood Volume, Cardiac Output, and Pulmonary Vascular Pattern in Mitral Stenosis*

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IT HAS previously been demonstrated that the central blood volume is not increased in mitral stenosis.[1,2,3] Furthermore, in the majority of cases, detailed x-ray studies of the pulmonary vasculature in mitral stenosis reveal a narrowing of the peripheral branches of the pulmonary arteries.[4–8] These observations are at variance with the expected findings, inasmuch as the pulmonary symptoms in mitral stenosis have traditionally been attributed to pulmonary engorgement.

In the following study an attempt has been made to relate the radiologic appearance of the pulmonary arterial tree to the calculated central blood volume and the cardiac output as determined by the dye dilution method.

MATERIAL AND METHOD

Fifty patients with uncomplicated mitral stenosis were selected for this study. Conventional chest x-rays were performed in all, and in 30 patients additional tomograms of the right lower lung field were obtained. For the purpose of assessing the changes, the pulmonary lung field was divided into three compartments: hilum, mid-lung field and peripheral lung field. Hilar arteries were classified as normal (N), increased (I), or markedly increased (MI). The size of the arteries in the mid-lung field and in the peripheral lung field was described as normal (N), diminished (D) or markedly diminished (MD).

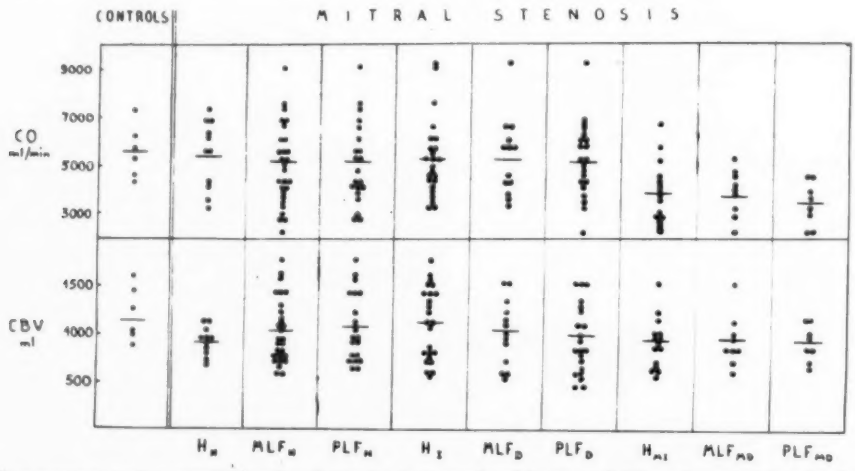

Fig. 1. Cardiac output and central blood volume in 6 normal subjects and 50 patients with mitral stenosis. The horizontal lines represent the average values.

Abbreviations: CO = cardiac output; CBV = central blood volume; H_N = normal hilar arteries; MLF_N = normal arteries in mid-lung field; PLF_N = normal arteries in peripheral lung field; H_I = hilar arteries increased; MLF_D = mid-lung field arteries diminished; PLF_D = peripheral lung field arteries diminished; H_{MI} = hilar arteries markedly increased; MLF_{MD} = peripheral lung field arteries markedly diminished; PLF_{MD} = peripheral lung field arteries markedly diminished.

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TABLE I

The Average Values of Cardiac Output, Central Blood Volume and the Central Blood Volume-Cardiac Output Ratio in 6 Controls and in 50 Patients with Mitral Stenosis, According to Their Pulmonary Vascular Pattern

	No. patients	Cardiac output (ml/min)	Central blood volume (ml)	$\frac{CBV}{CO} \times 100$
Controls	6	5,600	1,125	20.1
Mitral stenosis				
Hilar arteries				
Normal	11	5,450	915	16.8
Increased	24	5,270	1,120	21.2
Markedly increased	15	3,910	917	23.4
Arteries in mid-lung field				
Normal	28	5,140	1,031	20.1
Diminished	13	5,210	1,026	19.7
Markedly diminished	9	3,720	944	25.4
Arteries in peripheral lung field				
Normal	21	5,200	1,073	20.6
Diminished	21	5,160	995	19.3
Markedly diminished	8	3,450	910	26.4

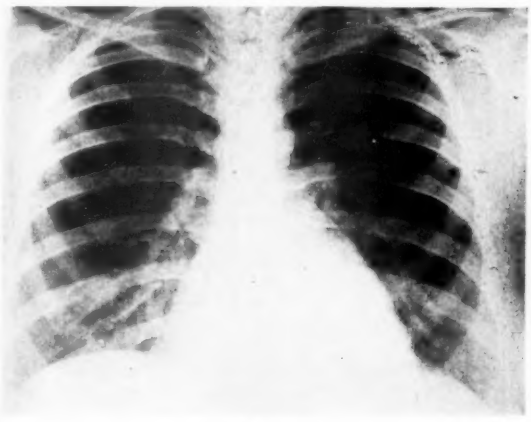
Determinations of the cardiac output and central blood volume were performed on the patients in a resting, fasting state, after receiving 0.1 g pentobarbital one hour prior to the examination. A No. 18 Cournand arterial needle was inserted into the brachial artery. Two ml of a 2 per cent Evans-blue dye solution (T-1824) were then injected as rapidly as possible into the contralateral antecubital vein with the arm supported at shoulder level. Serial arterial samples were collected every two seconds in dried, heparinized test tubes mounted on a disc rotating at a constant speed.[9] The samples were centrifuged and the dye concentration of the undiluted plasma was determined with a Unicam Spectrophotometer (SP600). The dye concentrations were then plotted against time on semi-logarithmic paper. The cardiac output was calculated according to the equations of Stewart[14] and Hamilton and associates.[11] The central blood volume was determined by the method of Stewart[10] and Ebert.[12] The values for central blood volume were expressed in milliliters, as well as in percentage of cardiac output.

Six healthy subjects served as controls.

Results

The results are summarized in Table I and Figure 1.

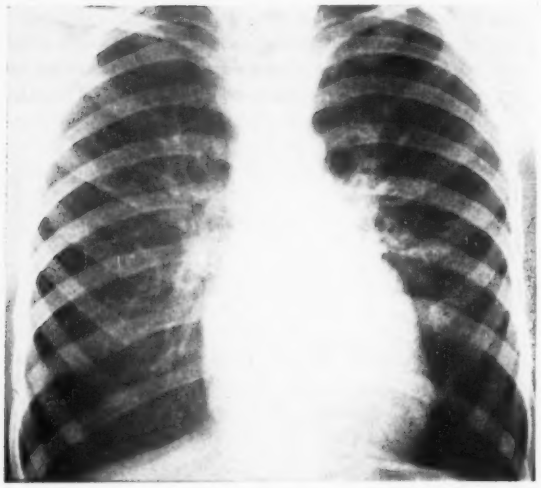
In patients with normal hilar arteries, the average cardiac output, central blood volume, and the ratio between these values were similar to those obtained in normal subjects. In patients with enlarged hilar arteries the average



2A

2B

Fig. 2. A 26-year-old female with mitral stenosis. (A) The conventional chest x-ray picture shows mitral configuration without enlargement of the heart shadow. The hilar arteries, the arteries in the mid-lung field and peripheral lung field are of normal size. (B) The tomogram demonstrates that the branches of the pulmonary artery follow a normal pattern.



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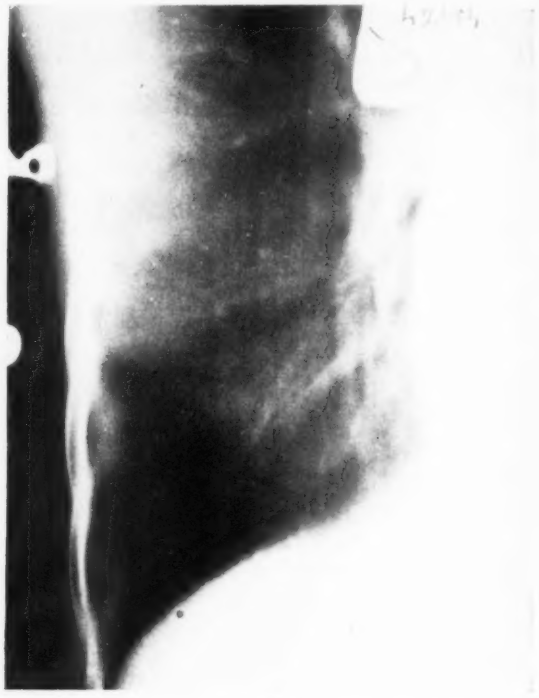

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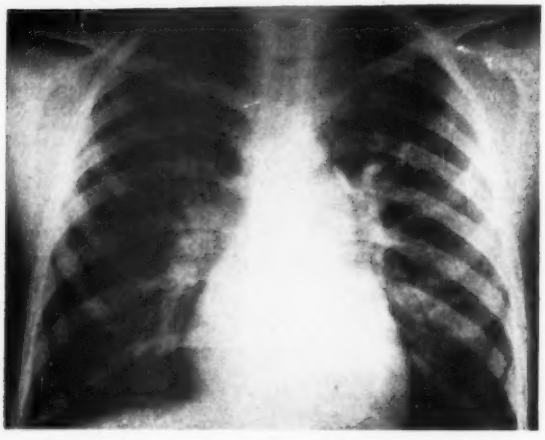
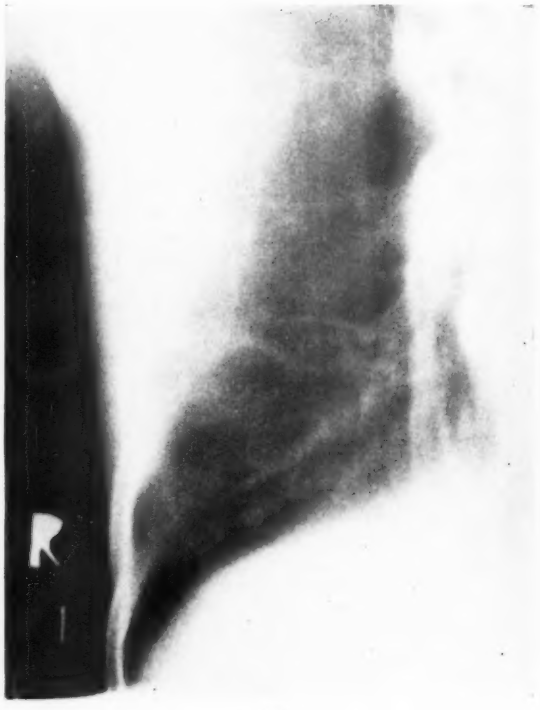
Fig. 3. A 15-year-old girl with mitral stenosis. (A) The conventional chest x-ray picture shows mitral configuration without enlargement of the heart shadow. The hilar arteries are enlarged. The peripheral vascular pattern is normal. (B) The tomogram demonstrates enlarged hilar arteries; the arteries in the mid-lung and peripheral lung field are normal.



4A



4B

Fig. 4. A 15-year-old boy with mitral stenosis. (A) The conventional chest x-ray picture shows mitral configuration with slightly enlarged heart shadow. The hilar-arteries are markedly enlarged. (B) The tomogram demonstrates enlarged hilar arteries. The arteries in the mid-lung field and peripheral lung field are narrowed and irregular.

cardiac output was normal and was not accompanied by significant changes in the absolute or relative values for central blood volume. In patients with markedly enlarged hilar arteries, the cardiac output was significantly diminished and the central blood volume, when expressed as percentage of the cardiac output, was found to be increased, although the absolute value of the central blood volume was almost identical with that of the controls.

Analogous results were observed when the x-ray appearance of the arteries of the mid- and peripheral lung fields was related to the cardiac output and to the central blood volume. A normal or diminished vascular pattern was generally accompanied by a normal cardiac output and a normal central blood volume, as expressed in both absolute and relative terms. In patients exhibiting marked diminution of the pulmonary arterial tree in the mid- and peripheral lung fields, a markedly decreased cardiac output was observed. This was associated with normal absolute values for the central blood volume, but with an increase in the central blood volume-cardiac output ratio.

Comment

Our studies show that in patients with mitral stenosis the cardiac output is normal when the roentgenologic appearance of the pulmonary vascular tree is normal or only slightly altered. It has been previously demonstrated that when there is a normal radiologic appearance of the lungs the hemodynamic alterations due to mechanical obstruction in the mitral valve area are either very slight or completely absent.[13,14] The present study indicates that there is a reduced cardiac output when the hilar arteries are markedly enlarged and the peripheral branches appear narrowed. In such patients hemodynamic data usually indicate an advanced stage of pulmonary hypertension. Further, the degree of narrowing of the peripheral arteries and the enlargement of the hilar arteries were found to be proportional to the severity of the pulmonary hypertension.[5,14]

The present study confirms the findings of other investigators that normal absolute values for central blood volume are encountered in mitral stenosis.[1,2,3] This observation holds true despite variations in the roentgenologic appearance of the pulmonary vascular tree. In contrast, in the presence of left ventricular failure as caused by other anatomic lesions, increased central blood volume has been reported.[1,2] This difference has been attributed to narrowing of the lumina of the pulmonary arterioles in mitral stenosis which is assumed to represent a protective mechanism against excessive rise of pressure in the pulmonary capillaries.[14–17] The presence of such a mechanism has not been yet demonstrated in left ventricular failure. It would be reasonable to assume that markedly enlarged hilar arteries contain more blood than normal-sized vessels, and that the central blood volume would therefore be increased. However, the concomitant constriction of the smaller arteries prevents overfilling of the more peripheral vessels of the lung. This may explain the nearly identical central blood volume observed in patients suffering from mitral stenosis of varying severity.

However, in calculating the central blood volume as the percentage of the cardiac output an obvious difference was evident between patients whose pulmonary vasculature was normal or only slightly altered and those whose hilar arteries were enlarged and whose peripheral pulmonary arteries were markedly narrowed. While in the first two groups this ratio was almost identical, being about 20 per cent of the cardiac output, in the latter group the ratio was increased to about 25 per cent. This change represents a relatively increased central blood volume when compared with the reduced blood flow.

Since most of the investigators reported normal values for central blood volume in cases of mitral stenosis, which may point to a narrowing of the smaller pulmonary arteries, as demonstrated in our x-ray studies, we believe that pulmonary vasoconstriction occurs more frequently than has hitherto been assumed.[16] Evidence for the presence of such a mechanism has also been obtained with the aid of various pharmacologic agents.[17–19]

Summary

In 50 patients suffering from mitral stenosis conventional chest x-rays were obtained. In 30 of

them additional tomograms of the right lower lung field were obtained. It has been shown in our series that the cardiac output is normal in the presence of normal or slightly altered pulmonary vasculature, while it is decreased in patients with enlarged hilar arteries and markedly narrowed arteries in the mid- and peripheral lung fields. The values for the central blood volume were within the normal range for all patients. The central blood volume was found to be about 20 per cent of the cardiac output in patients with normal or slightly altered pulmonary vascular pattern, and about 25 per cent in those whose hilar arteries were much enlarged and whose peripheral branches were markedly narrowed.

Acknowledgment

We are grateful to Miss Rina Berkowitz for technical assistance and to Miss Yehudit Doman and Mrs. Klara Rozsa for the laboratory work.

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Mitral Commissurotomy

Comparison of Clinical and Hemodynamic Results One to Three Years After Surgery*

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A NUMBER of long-term studies evaluating the practical end results and the underlying hemodynamic changes of mitral commissurotomy have been reported.[1–9] It is apparent from some of these studies that the subjective improvement of the patient following mitral commissurotomy cannot always be substantiated by corresponding objective findings. Bergy and Bruce[4] came to the conclusion that for some patients the term describes a change in attitude toward their disease and disability rather than improvement in cardiorespiratory function. On the other hand, Glover and co-workers[10,11] in an analysis of 50 patients studied five or more years following mitral commissurotomy stated that cardiac catheterization data paralleled or corroborated the observed functional state whether improved or unimproved. This is in agreement with Judson and co-workers[12] who found that, in general, symptomatic improvement paralleled improvement in cardio-hemodynamics or the renal function or both.

Many of the postoperative follow-up studies[2–4,11–15] have been based on clinical evaluation alone or, if cardiac catheterization was included, it wasoften done soon after surgery.[1,5,16–19] However, the patients' statements as to their improvement after mitral surgery have to be regarded with caution. Most of them had followed a steady downhill course before surgery and many of them had been cardiac cripples. Many patients were under better medical management after surgery with closer patient-doctor relationship and better insight into their disease and, therefore, better adjusted to it. With this in mind, it is not difficult to understand that frequently claims as to subjective improvement and exercise tolerance are exaggerated. It has been shown that physical examination, x-ray studies, and ECG do not always reflect hemodynamic changes.[1–3,10,14,17,20] Moreover, evidence presented suggests that hemodynamic improvement can take place for considerable time and that final conclusions as to the maximal clinical and hemodynamic benefit from surgery cannot be drawn for at least one year following surgery.

In view of these facts, we decided to follow our patients by yearly clinical evaluation and by cardiac catheterization before and possibly one or more years after surgery.

METHOD

The total number of patients studied was 93. Evaluation of the patient included detailed clinical history, physical examination, four position chest x-ray with barium swallow, electrocardiogram and phonocardiogram. All patients underwent right, and in addition some left, heart catheterization (more recent patients) before surgery. Right heart catheterization was performed in the usual fashion, left heart catheterization by the modified Biorck technic. Pressures were measured with Sanborn electromanometers and recorded with Sanborn Polyviso four channel recorder. Cardiac output was

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determined by the Fick principle. Mitral valve area was calculated by the hydraulic formula of Gorlin and Gorlin.[21] Mitral valve resistance and pulmonary arteriolar resistance were calculated by the following formulas:

$$\text{MVR (dynes sec cm}^{-5}) = \frac{\text{PVC mean (or LA mean)}}{\text{CO cc/sec.}} \times 1{,}332$$

$$\text{PAR (dynes sec cm}^{-5}) = \frac{\text{PA mean} - \text{PVC mean (or LA)}}{\text{CO cc/sec.}} \times 1{,}332$$

Surgery was recommended if pure or predominant mitral stenosis was diagnosed and if the patient was markedly incapacitated or followed a rapid downhill course. Of the patients thus studied and subsequently operated on, 33 consented to a second cardiac catheterization (the majority right, in more recent patients right and left) one or more years following mitral commissurotomy.

Results

Table I gives the clinical results in 93 patients who were followed one or more years following surgery. The majority of the patients were in functional group III preoperatively. Of the 74 patients living today, 55 improved following surgery and most of them advanced into a higher functional group. This represents a 59 per cent chance for this group of patients to survive and improve following mitral commissurotomy. The operative mortality was 12.9 per cent. This includes bad operative risk patients in functional group IV.

TABLE I

Pre- and Postoperative Functional Classification in 93 Patients

Functional class	Postoperative				Death rate	
Preoperative	I	II	III	IV	Operative death	Late death
I (0)	—	—	—	—	—	—
II (28)	10	13	4	—	1	—
III (54)	13	13	14	—	9	5
IV (11)	3	—	3	1	2	2
Total (93)	26	26	21	1	12	7

Correlation of Functional Classification and Catheterization Data

Pulmonary Artery Pressure: The symptomatic state of the patients as expressed by the functional classification of the New York Heart Association was compared with different hemodynamic parameters and with changes in x-ray and electrocardiogram. When pulmonary artery pressure is put in relation to the functional state (Fig. 1), irrespective of whether pre- or postoperatively, pulmonary artery pressure is

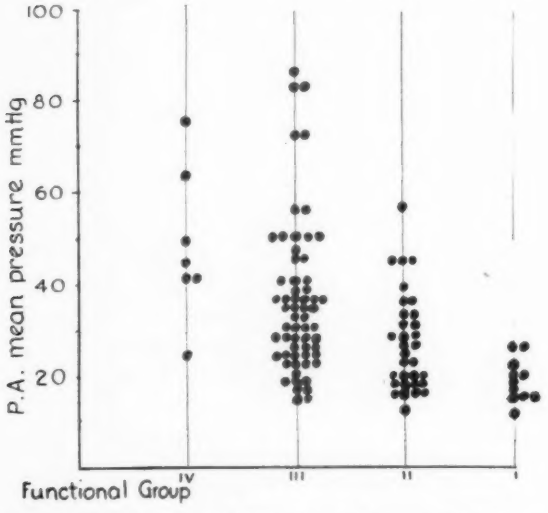

Fig. 1. Relation of pulmonary artery mean pressure to functional classification.

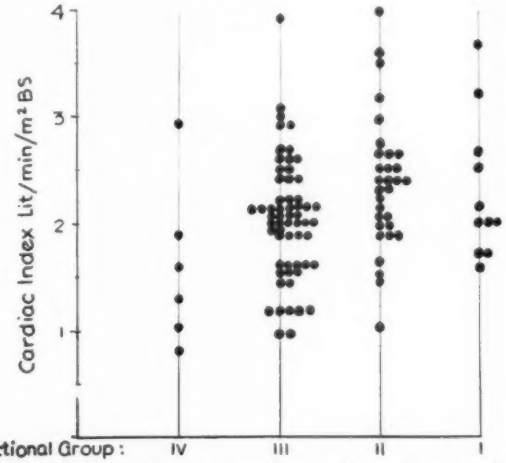

Fig. 2. Relation of resting cardiac index to functional classification.

lowest in group I and II patients. However, there is quite a scatter of the pressure in the different groups, indicating that symptoms and exercise tolerance are only partially related to pulmonary artery pressure.

Cardiac Output and Left Atrial Pressure: There was no significant correlation between the functional classification and the resting cardiac output as can be seen in Figure 2. While patients in functional group I and II have higher cardiac output than patients in functional group III and IV, the range of the individual points is even wider than that of the pulmonary artery pressure.

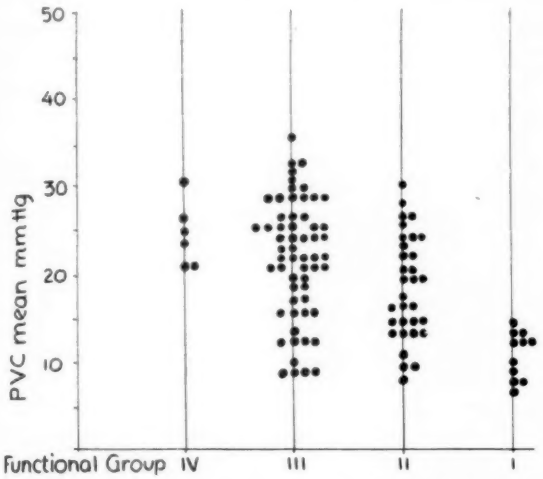

Fig. 3. Relation of capillary wedge pressure to functional classification.

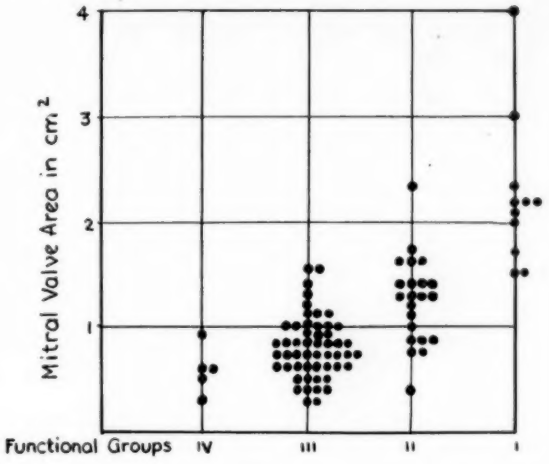

Fig. 4. Relation of mitral valve area to functional classification.

Pulmonary capillary wedge pressure or left atrial pressure shows a closer relationship to functional classification and thus to symptomatology (Fig. 3). The individual points are less scattered and all patients in functional group I have normal or close to normal resting mean pulmonary capillary wedge pressure.

Mitral Valve Area: The closest relationship to the functional classification is shown by the mitral valve area (Fig. 4). This indicates that in the patients with predominant mitral stenosis studied here, the obstruction at the mitral valve was closely related to the symptoms of the

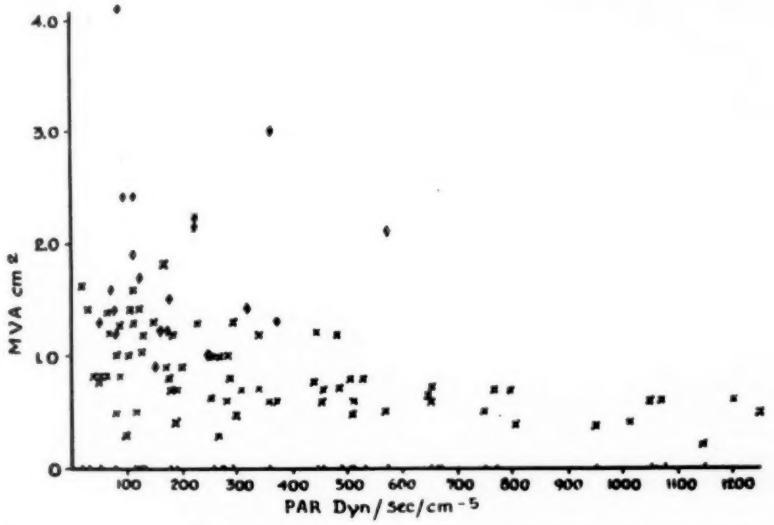

Fig. 5. Relation of mitral valve area to pulmonary arteriolar resistance before (×) and after (•) surgery.

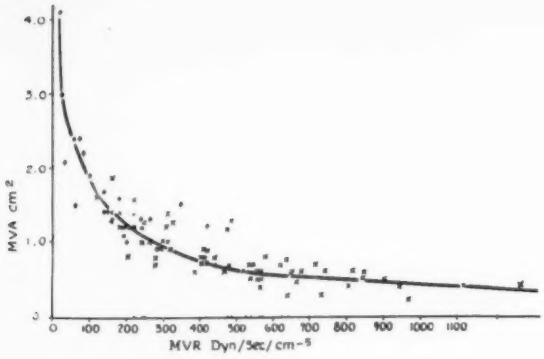

Fig. 6. Relation of mitral valve area to mitral valve resistance before (×) and after (•) surgery.

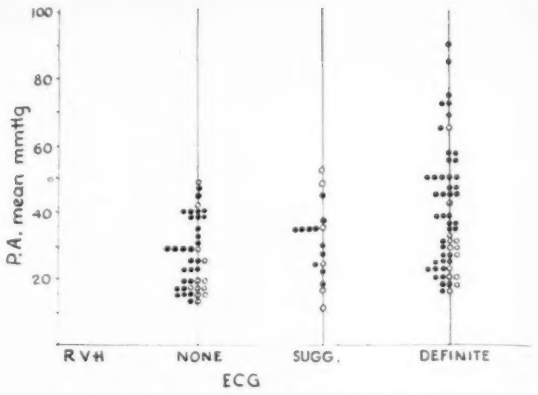

Fig. 7. Correlation of pulmonary artery pressure and RVH in ECG.

patients as expressed by the functional classification. All patients in functional group I showed a mitral valve area greater than 1.5 cm² while most of the patients in functional group III had a mitral valve area less than 1 cm². However, there are some patients who have relatively good mitral valve area and are in a lower functional group. The mitral valve area does not correlate well with the pulmonary arteriolar resistance as shown in Figure 5. Mitral valve resistance, on the other hand, is directly related to mitral valve area as shown in Figure 6.

Cardiac Enlargement: Comparison of cardiac enlargement by x-ray with the functional classification did not show good correlation. The transverse cardiac diameter, if enlarged preoperatively, decreased significantly only in an occasional case. Patients with good symptomatic improvement often maintained their cardiac enlargement.

Electrocardiogram: The electrocardiographic evidence of right ventricular hypertrophy could be related to the pulmonary artery pressure, as shown in Figure 7. However, since pulmonary artery pressure does not show good correlation with functional classification, the electrocardiogram does not seem to be a very good guide in judging the patient's disability. Furthermore, electrocardiographic changes tend to persist after operation even in patients with good clinical improvement.

CORRELATION OF POSTOPERATIVE RESULTS AND MITRAL VALVE AREA

Since the mitral valve showed the closest relationship to the functional state in the 93 patients observed, the patients studied by cardiac catheterization pre- and one to three years postoperatively were classified according to the postoperative mitral valve area. They were divided into three groups and hemodynamic and functional changes were compared with changes in mitral valve area following surgery. Group A includes 15 patients in whom the postoperative mitral valve area was greater than 1.5 cm² and no regurgitation was present (pre- and postoperatively). Group B includes 7 patients in whom the postoperative mitral valve area was less than 1.5 cm² either due to inadequate opening of the mitral valve or to restenosis but in whom no mitral regurgitation was present. Group C includes 11 patients in whom significant mitral regurgitation was present postoperatively and no mitral valve area could be calculated.

Group A. Valve Area Greater Than 1.5 Cm²: Patients in group A with postoperative mitral

TABLE II

Pre- and Postoperative Functional Classification in Group A (Valve Area > 1.5 cm²)

Functional class	Postoperative			
Preoperative	I	II	III	IV
I (0)	—	—	—	—
II (1)	1	—	—	—
III (12)	8	4	—	—
IV (2)	2	—	—	—

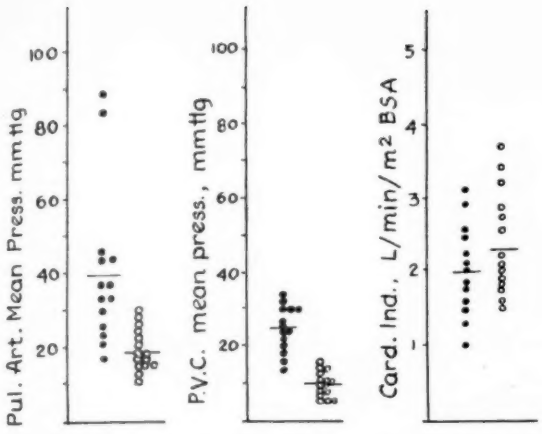

Fig. 8. Group A. Mitral valve area increased to 1.5 cm² or more. No insufficiency produced. ● Preoperative; ○ Postoperative; —— Average.

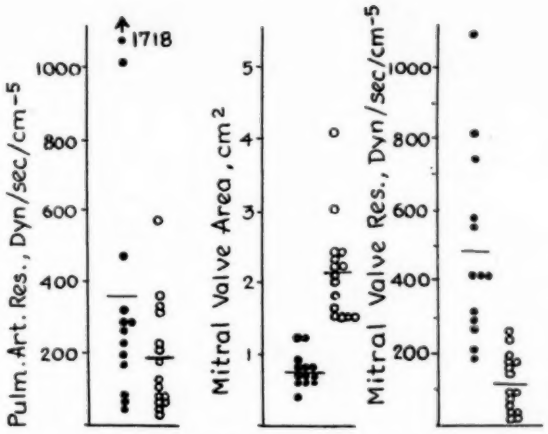

Fig. 9. Group A. Mitral valve area increased to 1.5 cm_2 or more. No insufficiency produced. ● Preoperative; ○ Postoperative; —— Average.

valve area greater than 1.5 cm² showed marked symptomatic improvement. Table II shows the functional classification before and after surgery. Two patients were in functional class IV before surgery, while following surgery they moved up to class I. Of twelve patients in functional group III before surgery, eight moved up to group I and four to group II. One patient in functional group II moved up to functional group I.

The mean pulmonary artery pressures decreased following surgery, many of them to normal levels, while some remained moderately elevated (Fig. 8). The pulmonary capillary wedge pressure was elevated in all patients and all but one returned to normal following operation. Cardiac output showed marked differences: Some patients had normal cardiac index while in others it was markedly decreased. The average was low. The marked scatter of the cardiac index is probably partially due to the fact that some patients were not in true resting state. The postoperative average cardiac output increased but the same wide range is present as preoperatively.

The average pulmonary arteriolar resistance showed a decrease following operation (Fig. 9). However, the presence of markedly abnormal resistance in some and normal in other cases before and after surgery indicates that this is a secondary phenomenon and arteriolar changes vary in different patients. All mitral valve areas were below 1.3 cm² before surgery and 13 of the 15 were below 1 cm². The valve areas increased to more than 1.5 cm² in all patients after operation and to more than 2.0 cm² in the majority. The mitral valve resistance decreased accordingly from abnormal preoperative levels to normal in all but two patients.

Group B. Valve Area Less Than 1.5 Cm²: Patients with less than 1.5 cm² mitral valve area postoperatively (group B) did not show much change in functional classification (Table III).

TABLE III

Pre- and Postoperative Functional Classification in Group B (Valve Area < 1.5 cm²)

Functional class	Postoperative			
Preoperative	I	II	III	IV
I (0)	—	—	—	—
II (3)	—	2	1	—
III (4)	—	1	3	—
IV (0)	—	—	—	—

Three patients were in functional group II before surgery. Two remained in II and one regressed to group III. Four patients were in group III. Three remained in group III and one moved to group II.

The pulmonary artery pressure was abnormally elevated in five of the seven patients before

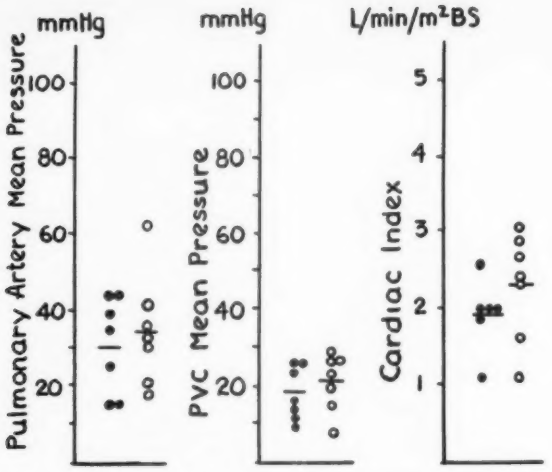

Fig. 10. Group B. Postoperative mitral valve area less than 1.5 cm². No regurgitation. ● Preoperative; O Postoperative; —— Average.

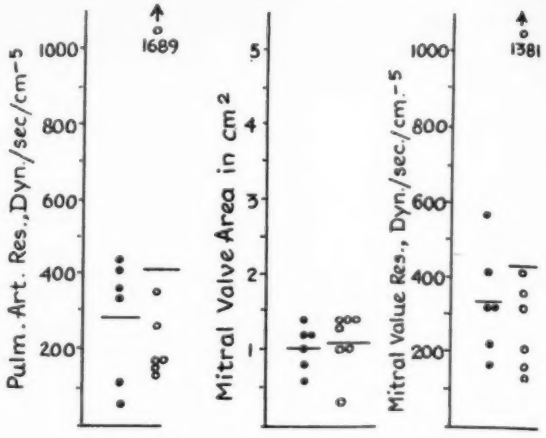

Fig. 11. Group B. Postoperative mitral valve area less than 1.5 cm². No regurgitation. ● Preoperative; O Postoperative; —— Average.

surgery (Fig. 10). Following operation, the pressures increased in all of the patients except one. The pulmonary capillary wedge pressure also showed an increase following the operation except in one patient. There was some increase in the cardiac output but this change was not significant. The pulmonary arteriolar and valve resistances increased following surgery (Fig. 11). The average mitral valve area remained the same, some patients having slightly greater, some smaller valve area than before surgery.

Group C. Mitral Regurgitation: Patients in group C who had significant mitral regurgitation postoperatively and in whom no mitral valve area could be calculated showed no significant changes in pulmonary artery, pulmonary capillary wedge pressure or cardiac output (Fig. 12). Three patients were in functional group II before surgery (Table IV). Two remained in II and one regressed to III. Of the eight patients in group III, two moved to II and six remained in III.

REASONS FOR FAILURE OF IMPROVEMENT

Group A: Since from the analysis of the total of 93 patients studied one would expect that all having mitral valve area greater than 1.5

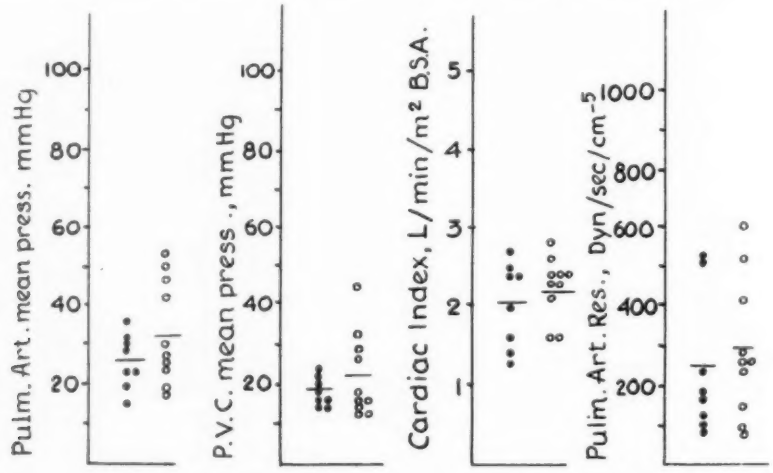

Fig. 12. Group C. Postoperative mitral regurgitation. ● Preoperative; O Postoperative; —— Average.

TABLE IV
Pre- and Postoperative Functional Classification in Group C (Mitral Regurgitation)

Functional class	Postoperative			
Preoperative	I	II	III	IV
I (0)	—	—	—	—
II (3)	—	2	1	—
III (8)	—	2	6	—
IV (0)	—	—	—	—

cm² would move to functional group I, we tried to evaluate the reasons why all patients in our group A did not move up to functional group I following operation. Three of the four patients remaining in functional group II had a postoperative mitral valve area of only slightly higher than 1.5 cm². One patient had a valve area of 2.4 cm². In the three patients with a postoperative mitral valve area of 1.6 cm², the persistence of moderate symptoms may be explained by the presence of the residual mitral obstruction and they may be considered as borderline cases in regard to hemodynamic improvement. However, two of the patients had marked cardiac enlargement with an increase of the transverse cardiac diameter of more than 50 per cent of the predicted normal which remained unchanged following surgery. In these cases, damage of the myocardium beyond repair can be considered as an additional factor working against maximal clinical improvement. One of the patients had a very good hemodynamic improvement with a mitral valve area of 2.4 cm², while functionally she moved from group III to group II. The heart showed no increase of the transverse cardiac diameter before and after surgery. The search for a cause of the residual symptoms in this patient revealed emotional problems and dependence on her cardiac disability as a possible factor.

Group B: In group B, one patient regressed from functional group II to functional group III. The analysis of the findings indicated that this patient had a smaller valve area postoperatively than before surgery. At operation, a good opening of the valve was reported by the surgeon. It has to be considered that this patient had a restenosis since clinical history indicated a transient improvement but later a decrease of the exercise tolerance. Another patient moved from functional group III to functional group II. The analysis indicated that this improvement was comparable with the hemodynamic changes in that this patient showed a moderate increase of the mitral valve area following surgery. Since this patient never had more improvement than at the time of recatheterization, it has to be considered as an inadequately opened mitral valve (postoperative valve area 1.5 cm²).

Group C: In the third group of patients with significant mitral regurgitation following operation, one patient regressed to functional group III. This patient had a marked mitral stenosis before operation and surgery removed the obstruction. However, marked insufficiency was produced which led to increase of the pulmonary artery pressure and decrease of the cardiac output. On the other hand, two patients who had regurgitation at the time of recatheterization moved from functional group III to II. Both patients had marked narrowing preoperatively while postoperatively the valve area could not be calculated because of the regurgitation. However, pulmonary artery and "PVC" pressures decreased while cardiac output increased and response to exercise was improved after the operation at the time of the second cardiac catheterization.

Conclusions

Our results confirm the findings of others[22] that the critical mitral valve area in pure mitral stenosis is around 1.6 cm². Patients having 1.6 cm² or greater valve area usually have no symptoms and are in functional group I. Pulmonary capillary wedge pressure or left atrial pressure, pulmonary artery pressure and pulmonary arteriolar resistance are lowest in functional group I. With decreased exercise tolerance, the pressures increase and the cardiac output decreases. However, there is quite a variation in these parameters in different patients. Sometimes patients in functional group III have close to normal resting pulmonary artery pressures, although the majority have moderately or markedly increased pressures and decreased cardiac output.

In general, the patient's symptomatic im-

provement parallels the hemodynamic changes if no regurgitation was produced. All patients having more than 1.5 cm^2 valve area improved markedly to moderately in all their hemodynamic findings. Patients who had no adequate opening or who restenosed and whose postoperative valve area was less than 1.5 cm^2 showed only slight or no improvement or further deterioration. It is felt that in some patients myocardial damage is advanced to such a degree that in spite of adequate opening of the valve, functional improvement is only moderate. In an occasional patient, good postoperative valve size does not correlate well with good functional improvement due to emotional dependence on cardiac disability. These emotional factors were studied by our group and will be published elsewhere.

Restenosis of the mitral valve does occur and was present in 6 per cent of our patients studied by cardiac catheterization.

Marked regurgitation following operation prevented good improvement even if obstruction was adequately relieved. Some patients, however, with moderate regurgitation postoperatively, will improve if the obstruction to flow is relieved. This would indicate that patients with predominant obstruction and mild to moderate regurgitation may benefit from surgery in a degree which correlates with the stenosis relieved and with the amount of postoperative regurgitation.

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Studies in Coronary Surgery

Coronary Heart Disease

Ballistocardiographic Evaluation of Surgical Treatment*

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By its very nature, coronary heart disease continues to defy "objective" evaluation. Aside from the obvious evidence offered by the presence of congestive heart failure, objective evidence for the degree of myocardial damage suffered by the patient who has convalesced from a myocardial infarct is difficult to obtain. Even more difficult is the objective determination of the degree of myocardial damage in patients with angina pectoris; and it has been virtually impossible to derive objective and graphic evidence of changes in myocardial function before and after cardiac surgery.

The ballistocardiogram as a method has been applied to most of these problems at different times. The obviously deteriorated BCG that persists after a coronary occlusion is accepted as an ominous sign. The return of the BCG pattern toward normal after an acute coronary episode is accepted as evidence for improved myocardial function and an improved prognosis.

Of particular significance are the classic studies of the Johns Hopkins group on the use of ballistocardiography in determining the stress effect of cigarette smoking in patients with coronary heart disease.[1–3] In a large series of carefully studied cases, the BCG was found six and one-half times more accurate than the electrocardiogram exercise tolerance test in confirming the previously proved diagnosis of coronary heart disease. While, admittedly, none of these changes is absolutely diagnostic, they were as a group sufficiently interesting for us to feel that the BCG could be profitably applied to the problem of evaluation of cardiac surgery for coronary heart disease.

Previous studies in which the BCG was used to follow changes caused by cardiac surgery have been concerned only with operations for rheumatic valvular disease and congenital heart disease. In many of these cases, the method has been found quite useful in evaluating the extent of anatomic correction achieved by the surgeon. This study is concerned with the functional changes in myocardial contractility following surgical operation for coronary heart disease.

METHOD OF STUDY AND MATERIAL

In a series of patients undergoing the Beck I operation for coronary heart disease,[4] direct body BCG's have been recorded in displacement, velocity, and acceleration. These records were obtained prior to operation and at regular intervals thereafter. This preliminary report is concerned with an evaluation of the ballistocardiographic changes in the first 17 patients in this series, who have now gone long enough to allow a long-term follow-up.

The final interpretation of the BCG's has been carried out by one of us (S. R. A.), independently, without reference to the clinical status of the patient. The displacement and velocity trac-

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TABLE I

Clinical Status, Pre- and Postoperative, of Consecutive Series of 17 Patients with Long-Term Ballistocardiographic Studies

Case	Age at time of operation	Years of follow-up since operation	Duration of symptoms prior to operation (years)	Number of clinical episodes of acute infarction		Severity and frequency of angina		Ability to work		General condition		Severity of myocardial destruction (as observed at operation)	Evaluation of result
				Pre	Post	Pre	Post	Pre	Post	Pre	Post		
1. R. M.	45	2 1/2	1	2	0	0	0	1	1	2	1	2	1
2. J. D.	57	2 1/2	2/3	0	0	4	1	4	1	4	1	1	1
3. A. N.	34	2 1/2	6	1	0	2	1	2	1	3	1	1	1
4. D. F.	43	2 3/12	1/2	1	0	3	2	3	1	3	1	2	1
5. W. W.	40	2 1/2	2/3	3	0	3	1	3	1	4	1	2	1
6. E. W.	52	2	3	1	0	3	2	3	2	3	1	2	2
7. G. F.	55	2	1 1/2	1	0	3	0	4	2	4	2	2	2
8. J. S.	46	2	5	2	0	1	0	4	2	4	1	3	1
9. H. C.	43	2	1	1	0	3	1	3	1	4	1	2	1
10. H. H.	37	2	1 1/2	2	0	2	2	2	1	3	2	3	2
11. H. K.	53	1 10/12	5	2	0	2	1	4	2	3	1	3	2
12. K. B.	50	1 10/12	7	3	0	2	1	4	1	3	1	4	1
13. I. K.	36	1 10/12	2	2	0	2	1	2	1	2	1	2	2
14. O. S.	50	*	4	2	1	4	2	4	2	4	3	2	*
15. W. K.	27	1 9/12	1	1	1	3	2	2	2	3	2	2	3
16. W. B.	55	1 1/2	7	1	0	2	1	4	2	3	2	2	2
17. B. J.	55	1 1/2	1/2	2	1	3	1	3	1	3	2	1	2

* Died suddenly 5 months postoperative.

Severity and frequency of angina: 1. little or none; 2. moderate; 3. moderate to severe; 4. severe, continuous.
Ability to work: 1. full time, no limitation; 2. full time, some limitation; 3. part time; 4. unable.
General condition: 1. excellent; 2. very good; 3. fair; 4. poor.
Severity of myocardial destruction (as observed at operation): 1. little or none; 2. small scar; 3. approximately 25% of left ventricle; 4. 50% or more.
Evaluation of result: 1. excellent; 2. good; 3. fair; 4. no good.

ings have proved to merit little consideration in this series. On the one hand, the displacement tracings were highly susceptible to artifacts introduced by respiration, body motion, and nervousness; and, on the other hand, they were relatively insensitive to the small, rapid, abnormal forces originated in the heart, which were clearly seen on the acceleration tracing. The velocity BCG was somewhat better than the displacement in both these regards, but was not so good as the acceleration. Therefore, only the latter will be given detailed interpretation.

The instrument used in this study has been described in detail elsewhere.[5] Simultaneous tracings of suitable ECG leads, heart sounds, and arterial pulse curves were recorded by means of a direct-writing, 4-channel Sanborn Polyviso.

Table I summarizes the pertinent clinical features in these 17 patients, with particular reference to their preoperative and long-term postoperative status. Of particular interest in this study is the unique opportunity for *direct* observations on the heart in patients undergoing operation for coronary heart disease, thus providing a heretofore unavailable experience in clinical and pathophysiologic correlation. The severity of myocardial destruction, as estimated at operation, is indicated in Table I.

TABLE II

Detailed Analysis of BCG's before Operation and at Latest Follow-Up

Patient	Preoperative							Late postoperative						
	Grade	Class (form)	I_a amplitude (mm)	R-I_a interval (sec)	JK time (sec)	Maximum IJ amplitude (mm)	Minimum IJ amplitude (mm)	Grade	Class (form)	I_a amplitude (mm)	R-I_a interval (sec)	JK time (sec)	Maximum IJ amplitude (mm)	Minimum IJ amplitude (mm)
1	I	B	3	0.11	0.18	6	3	I	B	3	0.12	0.15	6	6
2	II	A	2	0.12	0.09	8	15	I	A	3	0.11	0.10	5	4
3	I	A	5	0.14	0.11	12	9	I	A	3	0.09	0.10	12	9
4	I	B	3	0.16	0.16	7	7	I	B	5	0.13	0.18	9	9
5	II	B	4	0.14	0.18	8	4	I	A	3	0.09	0.11	11	8
6	II	C	–	0.11	—	5	3	I	A	2	0.12	.08	4	4
7	II	C	2	0.10	0.14	8	2	I	B	2	0.12	0.14	7	5
8	II	A	2	0.12	0.09	7	4	I	A	4	0.12	0.11	11	9
9	II	B	2	0.12	0.08	5	0	I	A	2	0.12	0.08	5	3
10	I	B	3	0.13	0.12	8	5	I	A	4	0.09	0.18	9	8
11	III	B	2	0.16	—	4	0	II	A	3	0.12	0.10	8	0
12	II	B	4	0.15	0.16	11	4	I	A	3	0.12	0.15	10	8
13	I	A	6	0.14	0.14	14	8	I	A	4	0.11	0.15	11	9
14	I	B	7	0.13	0.17	10	8	—	—	—	—	—	—	—
15	I	A	8	0.11	0.15	20	16	I	A	9	0.12	0.15	17	15
16	II	C	2	0.16	0.08	4	3	I	B	3	0.14	0.09	6	5
17	I	B	3	0.09	0.18	6	6	I	A	5	0.11	0.16	9	9

Results

Table II gives the detailed analysis of the preoperative and the most recent postoperative tracings in these 17 patients. Figures 1 to 5 are representative BCG's, along with simultaneous ECG tracings. In each figure, the displacement, velocity, and acceleration records are mounted in that order from above downward.

PREOPERATIVE STUDIES

The "objective" preoperative studies, including BCG, ECG, and cardiac fluoroscopy, merely confirm a notorious feature of coronary heart disease; namely, that there is no obligate correlation with reference to these studies, the actual condition of the myocardium, and the clinical status of the patient. Not infrequently, in patients with normal serial ECG's definite scarring and noncontractile areas of myocardium were demonstrated at operation. Although x-ray evidence of cardiac enlargement is generally a good index of extensive myocardial damage, in apparently normal-sized hearts similar degrees of muscle damage were frequently observed. The preoperative BCG, as anticipated, did not provide a very reliable index of the degree of myocardial scarring; and once again, it should be stressed that the BCG measures *function* and not *structure*.

Of the 17 patients in this study, the preoperative BCG was considered to be grade I in eight, grade II in eight, and grade III in one. Exercise and cigarette tests were also performed in many, but will be referred to only briefly in this paper.

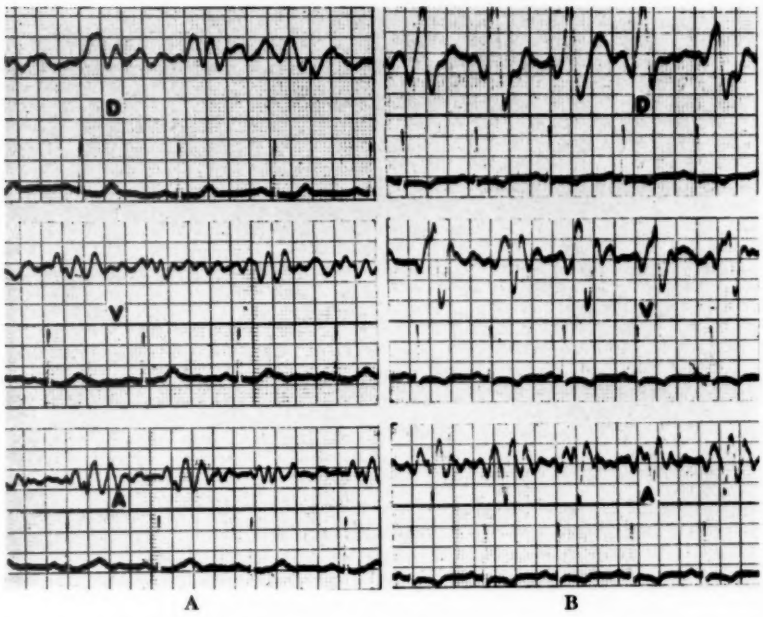

Fig. 1. Case 9. (A) A grade II preoperative record. (B) 14 days postoperative. Apparent immediate improvement. In this and in all subsequent figures the top BCG is displacement, middle is velocity, lower is acceleration, recorded simultaneously with an ECG.

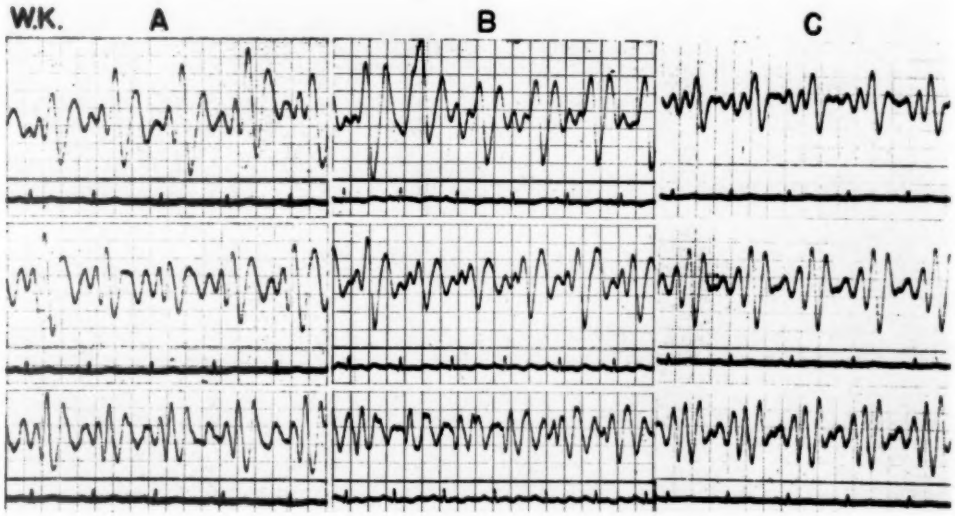

Fig. 2. Case 15. (A) A grade I preoperative BCG. (B) Less than a grade I, three and one-half months postoperative, but not an abnormal tracing. (C) Returned to a grade I, 20 months postoperative. The presence of a tall H wave (or early systolic wave) is noted in both the pre- and late postoperative acceleration tracings.

POSTOPERATIVE STUDIES

During the immediate postoperative period, the BCG usually deteriorated; presumably this was associated with the trauma of thoracotomy and the surgically induced pericarditis. In a few instances, however, there appeared to be immediate improvement in the BCG (Fig. 1). Generally, however, for the first three to six months after operation, precise evaluation of the BCG is difficult, and of doubtful reliability.

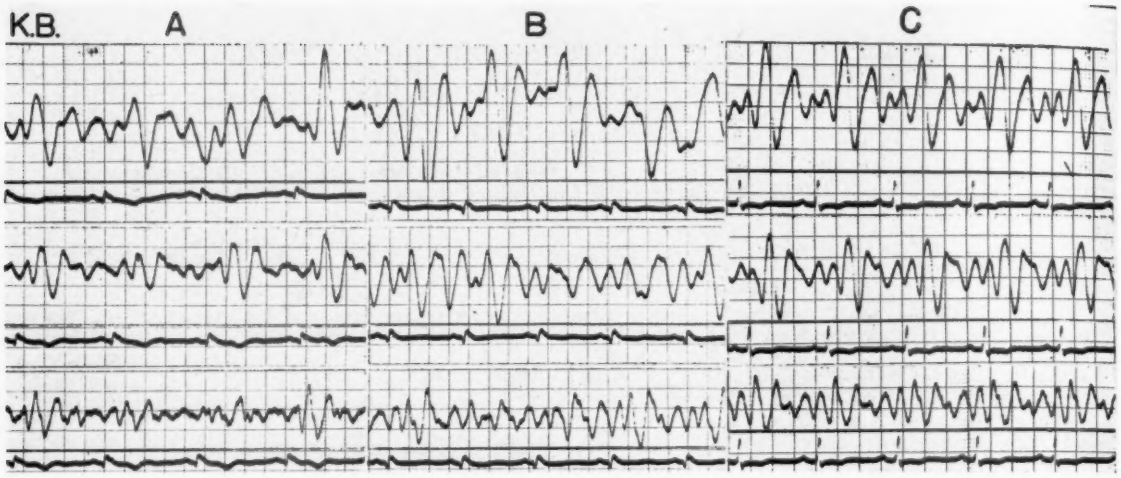

Fig. 3. Case 12. (A) Preoperative BCG grade II. Loss of both definition and amplitude of the BCG complex during the expiratory phase of respiration. (B) 10 days postoperative. Further deterioration to grade III. (C) Late postoperative. BCG now grade I. Peaks I, J, and K are clearly defined and the amplitude of the complex is well maintained during expiration. Note once again the large headward force preceding the I wave. This headward wave starts too early to be an H wave, which characterized many of the tracings in this series of patients with proved coronary heart disease.

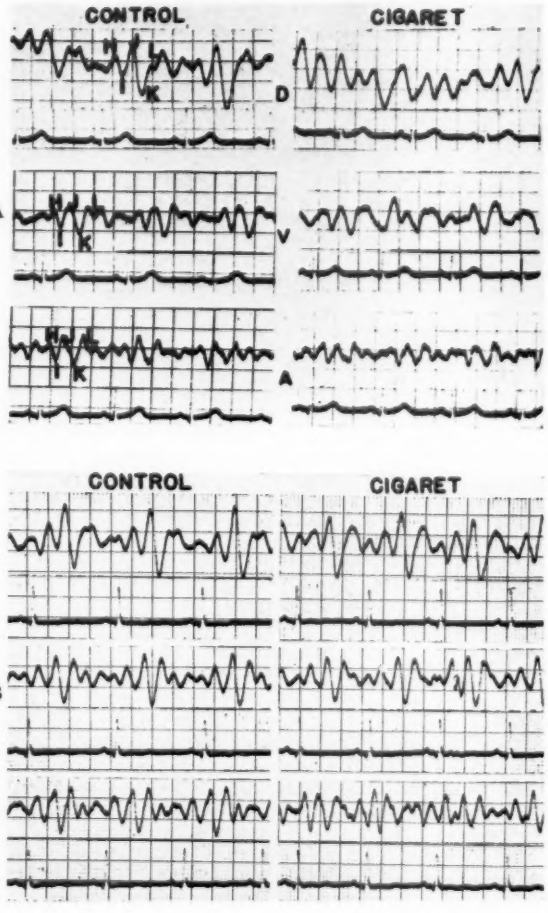

Fig. 4 (*right*). Case 4. (A) (upper). Control and post-cigarette tracing taken preoperatively, shows the manner in which smoking one cigarette accentuates the abnormalities found in the BCG. There is loss of amplitude, form, and definitiveness. (B) (lower). Same patient one year postoperative. The control tracing is much improved over the preoperative tracing, and the cigarette test does not cause the BCG to downgrade, but does introduce a notch in the I wave and several other complexes.

One year following operation, the BCG was interpreted as: grade I in 12 patients, grade II in three, and grade III in one patient. One patient had died. Subsequent further improvement is attested to by the fact that ultimately (two to three years postoperatively), 15 patients had become grade I, and only one was grade II.

At the time of the last follow-up, in three patients with essentially normal preoperative BCG's, there was no significant change (Fig. 2). In 11 patients with various degrees of preoperative BCG abnormality, there was definite improvement (Fig. 3, 4). In two patients, there was little or no BCG improvement over previous abnormalities.

Generally, there was good correlation between the BCG and the patient's clinical status. In no instance was there evidence that the op-

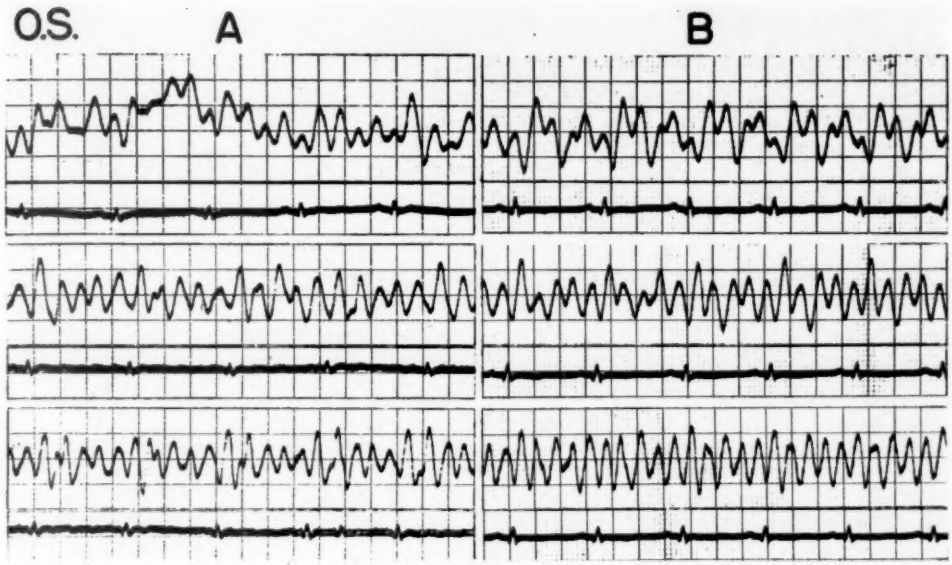

Fig. 5. Case 14. (A) Preoperative trace, although characterized as grade I because the amplitude of the complex is maintained during expiration, is, nevertheless, not a completely normal tracing. The large headward wave preceding the IJK complex is often of greater amplitude than it, and there is often seen a sharp notch on the I-J upstroke. (B) Six months postoperative record again demonstrates the early systolic wave, in many cases, larger than the BCG complex. The tracing is better in that the notch on the I-J stroke has disappeared, but is replaced occasionally by a slurred J peak. There are large amplitude waves seen through diastole, which is also not a normal finding. The patient died five days after this tracing.

erative procedure, per se, has caused long-term deterioration of the BCG.

The application of the cigarette test in demonstrating improvement is shown in Figure 4. In this patient, prior to operation, smoking one cigarette was associated with considerable deterioration of the BCG. One year after operation, the same stress had little effect on the BCG.

One patient (No. 14) died suddenly of an acute coronary occlusion six months after operation. A BCG, fortuitously obtained four days prior to death, though not normal, was better than that usually seen under these circumstances (Fig. 5).

Discussion

The significance of the ballistocardiographic improvement after operation certainly merits careful consideration. Conversion of an abnormal BCG into a normal one is readily demonstrated in many clinical states and physiologic experiments, which are quite analogous to the present study:

(a) Spontaneous improvement in the BCG coincides with recovery and convalescence from carditis, rheumatic or otherwise.

(b) Spontaneous improvement usually coincides with convalescence from a myocardial infarct.

(c) The abnormal BCG found associated with beri beri heart disease reverts to normal with vitamin and nutritional cure of the patient.

(d) A normal BCG deteriorates during an attack of angina pectoris.

(e) And, finally, when the normal BCG in a patient with coronary artery disease is made to deteriorate by a cigarette smoking test or an exercise tolerance test, it reverts back to normal soon after the stress is removed.

In all of these situations, the common denominator is improved contractility of the myocardium. It seems likely that this same factor is responsible for the improved tracings found in the patients herein presented.

In a fundamental sense, coronary heart disease is a grim tug-of-war, or battle for survival, between the relentless occlusive process on the one hand, and a compensating collateral circulation on the other. The patient who develops clinical evidence of coronary heart disease has arrived at this stage of precarious compensation. Any procedure which en-

hances the establishment of this collateral circulation *in advance* of the occlusive process in the coronary arteries should have far-reaching clinical benefit.[6]

Progression of the occlusive process in a coronary artery beyond a critical cross-sectional area (although not necessarily to complete occlusion) results in ischemia of a given area of myocardium, unless adequate collateral circulation is available for compensation. Death may occur, even without evidence of myocardial infarction, as a consequence of "electric instability" of the heart.[7] Myocardial infarction results when the blood supply is inadequate to maintain viability of the myocardium. At critical levels of compensation, myocardial *contractility* is seriously impaired, but *viability* is still maintained; so that an ultimate increase in collateral circulation then restores contractility with resultant improvement in systolic contraction of the heart.

Since by its very nature, coronary heart disease continues to defy "objective" evaluation, assessment of the benefit from any form of medical or surgical treatment for this disease is indeed fraught with peril (and always stimulates raging controversy). The natural reluctance of the physician to transfer laboratory results to the patient has reached its greatest development in the field of coronary heart disease.

No matter how brilliantly conceived and executed, no matter how scientifically sound and clinically impressive, every therapeutic advance against this disease has been plagued by necessary (but occasionally unreasonable) demands for "suitable controls." Obvious clinical benefit associated with procedures which have adequate laboratory substantiation have been categorically rejected, merely because human coronary heart disease cannot be reproduced *exactly* in the laboratory, or because its unpredictability defies simple statistical evaluation.

Of profound significance, then, is this demonstration of the application of the BCG as an apparently reliable "objective" method for the long-term evaluation of patients with coronary heart disease. Within the limits of this study, the problem of controls is obviated to some degree, in that each patient serves as his own control.

Summary and Conclusions

Long-term serial ballistocardiographic studies have been performed in 17 consecutive patients operated for coronary heart disease (Beck I operation). In 11 patients with some degree of preoperative abnormality, the BCG ultimately showed significant improvement. In three patients with essentially normal preoperative BCG's, there was no significant change. In two patients, there was little or no improvement over previous abnormalities.

Although this study of the BCG in a relatively small series of patients is admittedly of a preliminary nature, it appears to confirm previously reported impressive clinical results in patients operated for coronary heart disease. It is concluded that the changes in the ballistocardiogram reflect the improved contractility of the myocardium in a great majority of the patients operated.

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Changes in Peripheral Circulation in Lower Extremities Following the Beck I Operation for Coronary Heart Disease*

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THIS study was done because many patients stated that their feet were warmer after the Beck I operation for coronary heart disease.[1] Warming of the feet, if it occurred, would indicate a significant change in the peripheral circulation. This study was designed to document any such changes in these patients.

One of the first references to a relationship between coronary heart disease and skin temperatures was made by Doret and Ferrero[2] in 1951. These authors showed that the temperature was reduced over the areas of anginal pain radiation compared to temperatures elsewhere. Von Herbert[3] confirmed these observations and also showed that the temperatures rose over the area of pain radiation after cessation of pain. Hardy and Soderstrom[4] recorded skin temperatures in normal patients and found that under basal conditions, the average skin temperature of the foot was 31°C and of the lower leg, 33°. Stewart and Evans[5] showed that the basal metabolic rate and arterial blood pressure had no effect upon skin temperatures of the foot.

The true significance of skin temperatures was shown by Maddock and Collar[6] in 1933 by the use of the plethysmograph. These investigators showed that a definite relation existed between the skin temperature of the great toe and its blood supply. In 1948, Hardy and Soderstrom[4] studied the effect of room temperature on the relation between blood flow and skin temperature. They showed that below 29°C the skin temperature and blood flow were definitely related. This work was later confirmed by Fetcher *et al.*,[7] who in addition demonstrated that this relation failed to pertain above 32°C. According to these studies, a constant temperature room was not necessary as long as room temperature was below 28°C and did not vary more than 2°C in either direction during consecutive recordings. In 1950, Goetz[8] studied the relation between skin temperature, position of the extremity, and peripheral blood flow. Temperature rose when the foot was below the horizontal and fell when it was elevated. Macht[9] showed that two hours after the ingestion of protein containing glycine the skin temperature became elevated for a period of two hours.

METHOD

The study group consisted of two series of patients with coronary heart disease[10] who received the Beck I operation. The two series were studied separately by each of the authors, but since separate tabulation and evaluation of the data obtained produced similar results, the two series are combined for presentation. The control group consisted of patients who had other cardiac operations.

Skin temperatures of the feet before and after operation were measured using a standard thermocouple. Repeated measurements, made on an average of nine different days, were obtained to produce significant average figures. These were made in the patient's room, three to six hours after meals, and following a 40 to 60 minute equilibration time during which the patient was kept supine in bed, was not allowed to smoke, and the legs were uncovered from mid-thighs down. Blood

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pressure and body temperature measurements were made with each set of recordings. The humidity was not measured, but no measurements were made on excessively humid days. Figure 1 represents the approximate

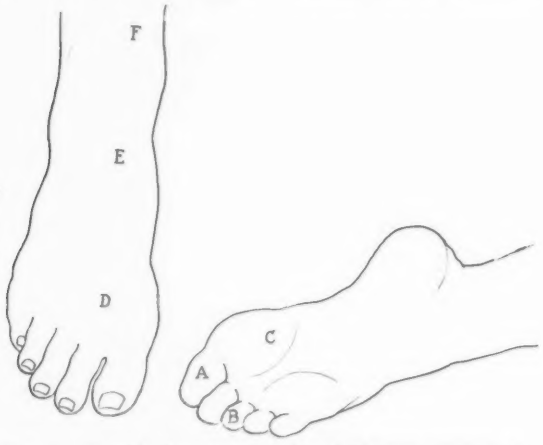

Fig. 1. Sketch showing dorsal and plantar aspects of the foot. The letters represent the approximate location of temperature measurements.

location of the six arbitrary points of temperature recordings. In accord with the work of Hardy and Soderstrom previously mentioned, no attempt was made to use a constant temperature room or to regulate the room temperature. It was found that the room temperature varied by only 2° from the average of 25°C. The McKesson dermatherm used was designed with variable setting control to compensate for the existing room temperature. It was felt that this method could detect significant changes and, therefore, more delicate methods were not necessary.

A thorough clinical investigation of each patient was done and included basal metabolic rate, past medical history, presence of previous infarct, presence or absence of failure, electrocardiogram, serum cholesterol, apprehension graded 1 to 4, and anginal pain graded 1 to 4 on the basis of physical activity and the medication required.

In addition to these clinical studies, the heart was examined at the time of operation to determine the degree of atherosclerosis of the coronary arteries and the presence or absence of infarct. This examination yielded information not obtainable by any other means of clinical study.

Results

A sustained average increase of 2°C or more during the two-week period after operation was considered by us as significant. "Normal ranges" of values were considered to be those averaging over 30°C, while those below this level were considered "subnormal." In actual practice, however, the "subnormal" values were usually below 28°C while the "normal" levels were usually above 32°C.

Measurements were made on a total of 46 patients with coronary heart disease (22 in series I and 24 in series II). According to the above classification, 23 patients were found to have normal temperatures before operation and 23 had subnormal values.

Patients with normal temperatures before operation

Repeated measurements were made on these patients according to the method described above. These measurements showed a remarkable uniformity with fluctuations from day to day throughout the entire study period of less than 2°C and often less than 1°C. None of these patients with normal temperatures before operation showed a significant change in temperature after the operation. Average determinations of temperatures in the entire group are given in Table I.

Patients with subnormal temperatures before operation

In this group the average temperature before

TABLE I

Average Values in Degrees Centigrade for 23 Patients Who Demonstrated No Postoperative Changes in Skin Temperature, Taken over Six Points on Foot (A to F)

Before operation					
A	B	C	D	E	F
31	31	32.6	32.6	31	31
31.7	30.8	32	32.2	31	31
31.5	31.3	32.6	32.8	31.2	31.2

After operation						
Post-operative day	A	B	C	D	E	F
1	32	31.9	32	32	31.2	32
4	31	30.8	32	30.8	31.8	31
7	31.6	30.8	32.2	31	31.3	31
10	32	31	32.4	31.4	31	31
14	32	31.2	32	32.2	32	31.2

operation was 26°C with a range from 23.5° to 29°C. Many of these patients gave a history of cold feet for some time before operation, frequently dating the onset at the time of first anginal episodes. As in the preceding group, these patients also showed a definite uniformity in temperature recordings from day to day. We feel that this uniformity indicates the absence of other uncontrolled factors or variables that could influence the results.

Of this group of 23 patients, two showed no temperature changes after the operation and had no subjective changes referable to the feet. Of the remaining 21 patients with subnormal values before operation, all showed a definite sustained increase in temperature after operation. Average temperatures for this entire group are presented in Table II. The average

TABLE II

Average Values in Degrees Centigrade for 21 Patients Showing Sustained Postoperative Increase in Skin Temperature of Lower Extremities

Before operation					
A	B	C	D	E	F
25.8	26	27	27	31	31
26.5	25	27	27	31	30
26	26	27.3	27.6	31.5	31

After operation						
Post-operative day	A	B	C	D	E	F
1	30	29.8	31	32	35	35
4	30.1	28.2	29	29.3	30	31
7	30	30.2	31	31	32.1	33
10	31	31	32	32.2	32.3	33.2
14	32	33	32.8	33.2	33.8	33.6

increase in temperature for the group was 4° to 5°C, with an individual average increase ranging from 2° to 10° C (Table III).

Analysis of the coronary groups as to correlation with other clinical data obtained on each patient revealed several interesting facts. In general, those patients with normal temperatures before and after the operation tended to be those with past history of myocardial infarction especially within the past two years. These patients as a group had very little or no anginal pain and showed average cholesterol values definitely higher than the group showing an increase in temperature after operation (Table IV). In contrast to this group, those patients with a definite sustained increase in skin temperatures were those with no history of infarct. This group tended to have moderate to quite severe angina and showed average cholesterol values definitely lower than the preceding group (Table V).

In the light of this correlation it is interesting to note that each of the two coronary patients with subnormal temperatures before operation, who failed to show an increase in temperatures following the operation, had a history of myocardial infarct within one year prior to the operation. Neither of these patients had any angina and their cholesterol values were both above the average value for the group showing a definite rise in temperature.

TABLE III

Patient with the Greatest Skin Temperature Rise in Degrees Centigrade

Before operation						
Pre-operative day	A	B	C	D	E	F
1	24	25	25	24	30	30
2	24	25	25	25	29	30
3	25	25	25	25	30	30

After operation						
Post-operative day	A	B	C	D	E	F
1	30	30	31	30	33	34
4	29	30	29	30	34	34
7	35	34	34	35	34	34
14	35	35	33	34	34	33

TABLE IV

Twenty-five Patients with Normal Skin Temperatures Before and After Operation

Patient	Age	Angina	Cholesterol	Time since history of last infarct	Electrocardiogram
GM	46	++	197	2½ yr	Atrial hypertrophy—RBBB
TO	59	0	293	7 yr	Anterior infarct
EV	50	+	280	1 yr	Old infarct
LH	45	0	186	3 yr	Normal
HS	42	+	259	1 yr	Anterolateral infarct
WE	67	++	300	1 yr	Inverted T waves
HD	56	++	387	3 yr	Old anterior infarct
HW	54	0	261	2 yr	Normal
LR	50	+	270	2 yr	Old anteroseptal infarct
JH	55	++	410	None	Old posterior infarct
EP	40	0	300	1 yr	Normal
WH	35	0	260	1 yr	? Old infarct
AE	34	++	356	1 yr	Normal
RS	48	+	306	6 mo	Left ventricular hypertrophy, T changes
SP	56	+	387	4 mo	Old anteroseptal infarct
JJ	35	++	350	1 yr	Old posterior infarct
AK	44	++	484	9 mo	Old infarct—LBBB
EO	30	++	398	1 yr	Slight ST changes
MF	44	+	331	1 yr	Remote posterior infarct
DH	44	+	320	1 yr	Remote posterior infarct
AD	57	+	390	4 mo	Slight ST depression V_{5-6}
BH	27	+	207	6 mo	Old posterior infarct
IH	43	++	346	1 yr	Old anterior and posterior infarcts
GD	56	+	247	4 mo	Recent anterior infarct
JS	35	+	350	4 mo	Recent anterior and septal infarct
Average	46	+	307	1⅓ yr	

No correlation was found with any of the other clinical data obtained on each patient. In particular there appeared to be no relationship whatsoever between the evaluation of apprehension and skin temperatures either before or after the operation.

PATIENTS UNDERGOING OTHER CARDIAC OPERATIONS

This group consisted of 14 patients in the following categories:

Eleven patients operated on for correction of mitral stenosis, one of whom also had proved coronary disease and low skin temperatures before operation (average temperature 27° C).

One patient with aortic stenosis corrected through left ventricular approach.

One patient undergoing closure of interatrial septal defect.

One patient with coronary heart disease and diabetes who received thoracotomy only.

Of this group, four patients showed normal values before the operation and no change after the operation. Of the remaining ten who showed subnormal levels (averaging 27°C) before operation, all showed a significant rise in skin temperature within 36 hours after operation to "normal" values averaging 32°C. In contrast to the sustained rise of the coronary patients, however, these subjects all showed a variable but definite drop to the original subnormal levels by the seventh to tenth day after operation. Average temperatures for this group are given in Table VI.

The patient with coronary disease and diabetes in the control group was considered significant since he showed a course of temperatures similar to the above. This patient was anesthetized, the chest was opened, but the heart was irritable and had transient episodes of ventricular tachycardia. The operation was

TABLE V

Twenty-one Patients Showing Sustained Average Increase in Skin Temperatures

Patient	Age	Angina	Cholesterol	Time since history of infarction	Electrocardiogram
EB	52	++	262	None	Normal
MH	43	+++	240	None	Normal
MF	55	+++	228	None	Normal
JW	58	+++	202	None	Notched P waves
JB	48	++−+++	278	8 yr	Old posterior infarct
JM	50	+	224	2½ yr	Old infarct
TM	50	+++	311	? 2 yr	Normal
TS	51	++	270	4 yr	Old infarct
HC	53	+++	291	None	? Old infarct
AG	50	+++	288	None	Slight ST elevation
MI	52	+++	278	None	Normal
RP	49	++++	216	4 yr	1st degree AV block
MP	47	+++	323	None	1st degree AV block
AS	60	+++	244	10 yr	Low voltage
SC	35	++++	329	2 yr	Old infarct
JM	45	++++	303	2 yr	Old infarct
SG	63	+++	255	None	Normal
JS	55	+++	340	None	Normal
RC	57	++++	180	None	RBBB
RS	50	+++	251	? 2 yr	Left axis deviation
Average	48½	+++	253	None or over 2 yr	

TABLE VI

Average Values in Degrees Centigrade for 10 Patients with Subnormal Skin Temperatures Preoperatively Demonstrating Only Transient Elevations Following Other Cardiac Operations

Before operation

A	B	C	D	E	F
26.5	26.2	26	26.6	27.2	28
27	26	26.4	26	27	27
26.4	26.5	26	26.2	27	28

After operation

Postoperative day	A	B	C	D	E	F
1	32.2	32	32	32.2	32	32.2
4	30	28.4	29	30	30	30
7	28	27.2	27	27.8	28	29
10	27.5	26	26	26	27	28
14	26.2	26	26.4	26.6	27	28.2

not done and the chest was closed. The foot temperatures rose from 26° before operation to 30°, but returned to the former level within one week.

Discussion

The temperatures reported here indicate that during the process of undergoing the Beck operation for coronary heart disease, changes take place causing a sustained rise in skin temperatures of the feet, provided a subnormal temperature was present before operation. These observations have special significance in that they represent actual measurements and have no subjective characteristics such as relief of pain after operation. The presence of arterial spasm as the cause of subnormal skin temperatures in coronary heart disease was postulated by Doret and Ferrero.[2] In the absence of cold feet before operation, which presumably means the absence of arterial spasm, there was no significant or sustained rise in foot temperatures. A definite vasospastic element appears to be present peripherally in patients

with moderately severe angina and no recent history of myocardial infarction. The alleviation of this spastic element is apparently found after myocardial infarction and after Beck I operation.

The problem of the etiology of this spasm is difficult; whether it is humoral or neurogenic, whether the result of pain or the effects of ischemic cardiac muscle remains unsolved. However, it is noteworthy that no matter what the exact etiology may be, vascular insufficiency to the myocardium appears to have an effect. It is possible that infarction of the heart destroys the ischemic area, thus alleviating pain and peripheral vascular spasm. Beck I operation apparently also alleviates the peripheral component of the disease. However, unlike the former, there is no demonstrable damage to the heart muscle, and it is postulated that the effect might be the result of restoring a sufficient blood supply to the ischemic myocardium.

It is of interest that the two patients with severe angina and proved atherosclerosis of the coronary arteries who underwent thoracotomies for other reasons had no relief of their peripheral vascular spasm, but on the other hand felt that their angina pectoris had improved somewhat. These can be considered in the same category as sham operation without the operation for coronary heart disease.

Conclusions

(1) In patients with subnormal skin temperatures before operation, open thoracotomy or anesthesia often results in increased skin temperatures in the feet within 36 hours after operation.

(2) After the Beck I operation for coronary heart disease (in 21 out of 23 patients) the rise persisted and increased during the two-week hospital period after operation. After various other operations on the heart, this elevation in temperature was sustained for several days only, returning to former cold levels within 1 week to 10 days. Therefore, none of the control group patients showed a sustained rise for the two-week hospital period after operation.

(3) If the skin temperature of the feet is normal before operation there tends to be no change in the foot temperature after operation.

(4) It is reasonable to speculate that the rise in temperature is due to a release of peripheral arterial spasm by the operative procedure. In the patients with coronary heart disease, this is an objective result of operation and has no relationship to relief of pain.

(5) This investigation verified observations of other investigators that blood pressure, basal metabolism rate, and rectal temperature, until above 38.5°C, have no effect on the skin temperature of the feet.

(6) Those patients showing a definite rise in skin temperature following operation tend to be those with no past history of myocardial infarction, with moderate to severe angina, few electrocardiographic changes, and only mild elevation in cholesterol. In contrast, those with no change in temperature after operation tend to be patients with a history of old myocardial infarction, relatively major electrocardiographic changes, mild to absent angina, and relatively high cholesterol values.

(7) The full meaning of the above observations must wait for further investigation, including prolonged follow-up studies. They do, however, indicate a definite relation between coronary disease and angina pectoris and peripheral arterial spasm that in some way appears to be released by the operative procedure.

Acknowledgment

The authors wish to express their gratitude to Dr. Claude S. Beck for his encouragement and many invaluable suggestions during the course of this investigation.

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An Evaluation of Three Revascularization Procedures in the Rehabilitation of the Coronary Patient

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CONFUSION and disagreement concerning the value and effectiveness of the surgical treatment of coronary artery disease characterize the pertinent current medical literature. The medical skeptic claims that good surgical results are due simply to coincidental spontaneous improvement, psychotherapeutic response to the scalpel, or concealment of the disease by surgical ablation of sensory pathways. He even vaguely infers that occasionally postsurgical infarction accounts for the disappearance of the angina.

This presentation records a small but significant series of patients with advanced coronary artery disease treated surgically. Initially, this series was limited to a group of class III and IV coronary cripples. The marked severity of illness and incapacity served as a baseline from which to measure postoperative improvement. The selected anginal cases presented the features of a fixed, unfavorable course with a long history of therapeutic frustration, progressive increasing symptomatology, and increasing cardiac functional impairment. Many had frequently recurring acute pulmonary edema, severe pain terminating in syncope, marked pulmonary emphysema, aneurysmal dilatation of the left ventricle, and moderately severe diabetes. At least 50 per cent had definite cardiomegaly. Furthermore, the natural history of this disease with these features is progressive and usually fatal.[1] Only an exceptional case spontaneously ceases to deteriorate.

RESULTS OF SURGERY

Three different operative procedures were performed over a three-year period, 1954 to 1957. These were cardiopexy with talc (Thompson), internal mammary artery ligation, and the Beck I procedure.

CARDIOPEXY

In the first series cardiopexy was performed in 17 cases of advanced coronary artery disease. Their ages ranged from 33 to 71 years. Eleven had definite evidence of previous myocardial infarction, all confirmed by electrocardiograms. There was only one female patient in this group.

TABLE I

Clinical Features in 17 Cases Subjected to Cardiopexy

Angina at rest	9
Angina on effort	2
Protracted coronary insufficiency	10
Previous myocardial infarction	11
Emphysema	6
Diabetes	2
Cardiac enlargement	9
Ventricular aneurysm	1
Heart failure	7
Acute pulmonary edema (recurrent)	3
Luetic aortitis with aortic regurgitation	1

Table I tabulates some of the clinical features. Duration of disease before surgery varied from two to five years. Those with longer duration demonstrated more unfavorable features including cardiomegaly, congestive failure, acute pulmonary edema, and bouts of protracted coronary insufficiency.

In Table II are tabulated our results with cardiopexy. It can be seen that an excellent

TABLE II
Results of Cardiopexy

Functional classification	Number of cases	Results				
		Excellent	Good	Fair	Poor	Expired
IV	9	5	1	0	1	2
III	8	6	0	1	0	1
Total	17	11	1	1	1	3

Excellent denotes complete or almost complete loss of angina.
Good denotes at least 50 per cent reduction of angina and 50 to 75 per cent reduction of nitroglycerin need.
Fair denotes 25 to 50 per cent improvement of pain and nitroglycerin need.
Poor denotes no improvement of angina and nitroglycerin need unchanged.

clinical result, as judged by a complete or almost complete disappearance of anginal pain, was obtained in almost two-thirds of the 17 cases.

Fatal Cases: Of the three deaths listed one constituted an operative mortality. He was a 56-year-old white male with two definite myocardial infarctions within 30 months and a probable third infarction of recent origin. His angina had been progressive for three months prior to surgery and he was apprehensive and depressed because of no response to intensive medical therapy. He died suddenly 48 hours after surgery. Autopsy revealed marked coronary sclerosis with old myocardial infarction and fresh scattered areas of subendocardial infarction.

A late postoperative death occurred in a 44-year-old white male who had his first myocardial infarction at the age of 39 years, the second at age 42. Cardiopexy was performed because of increasing angina. Death occurred six weeks postoperatively due to renal shutdown following hematuria secondary to anticoagulant therapy for phlebitis.

The other late death occurred in a 72-year-old white male who expired with an acute myocardial infarction six weeks after discharge from the hospital.

Illustrative Cases with Excellent Results: A 54-year-old male had an extensive anterior wall infarction confirmed by electrocardiogram in September, 1954. He developed angina in March, 1955, which was progressive. Electrocardiograms on November 1, 1955, showed severe coronary insufficiency as manifested by

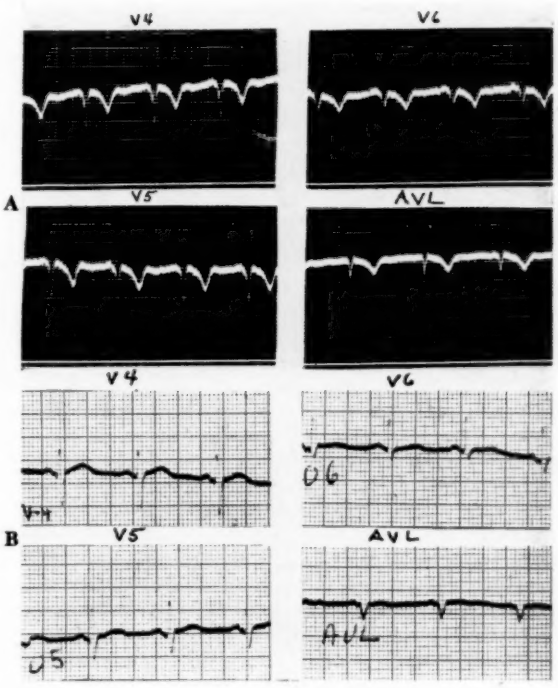

Fig. 1. Electrocardiograms before and after talc cardiopexy performed on November 15, 1955. (A) November 1, 1955. (B) November 25, 1955.

deeply inverted T waves in leads aVL, V_4 to V_6 (Fig. 1A). Talc cardiopexy was performed November 15, 1955. The electrocardiogram 11 days later revealed correction of his severe coronary insufficiency pattern (Fig. 1B).

Another case with angina decubitus and distinct electrocardiographic evidence of chronic coronary insufficiency (Fig. 2A) was much improved by surgery. The electrocardiogram

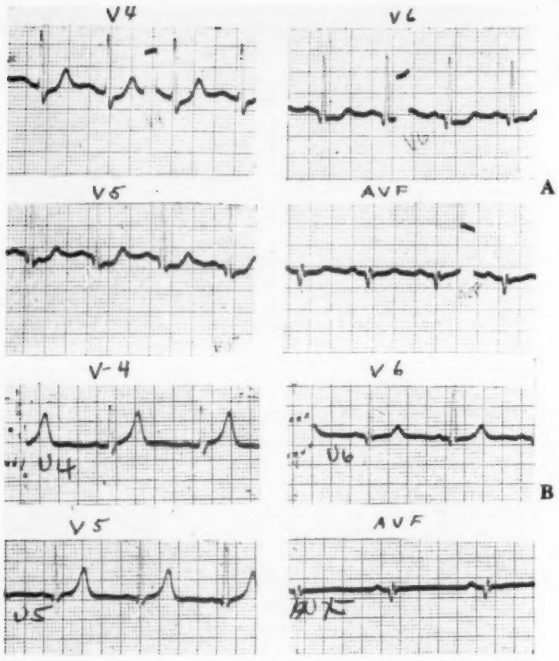

Fig. 2. Electrocardiograms before and after talc cardiopexy performed on November 9, 1955. (A) September 30, 1955. (B) November 15, 1955.

also improved (Fig. 2B). Although the electrocardiographic improvement may be secondary to the traumatic pericarditis, it also may be produced by improved myocardial blood flow.

In another case with dramatic improvement a reduction of cardiomegaly was demonstrated while the patient was still actively working as a farmer (Fig. 3).

One patient with a very extensive anterior wall infarction in October, 1953, was able to return to work in February, 1954, but soon developed angina which became progressively more severe and totally incapacitated him. On August 6, 1954, cardiopexy was performed and he made an abrupt dramatic recovery. Within one month he returned to his work which involved some manual labor. He has continued to work without any angina for over three years. Electrocardiograms have demonstrated extensive anterior wall infarction with persistent ST segment elevation suggestive of aneurysm. During this three-year period his fluoroscopic and x-ray examinations showed the gradual development of a ventricular aneurysm.

Follow-up: Thirteen patients have survived for one and one-half to three years after surgery. Eleven are completely rehabilitated and maintain good to excellent clinical improvement. The majority do not require cardiac medications.

With regard to longevity, this series closely parallels the experiences of Beck and Brofman. In evaluating the Beck I procedure, Brofman[2] in a long term follow-up on 137 cases over a

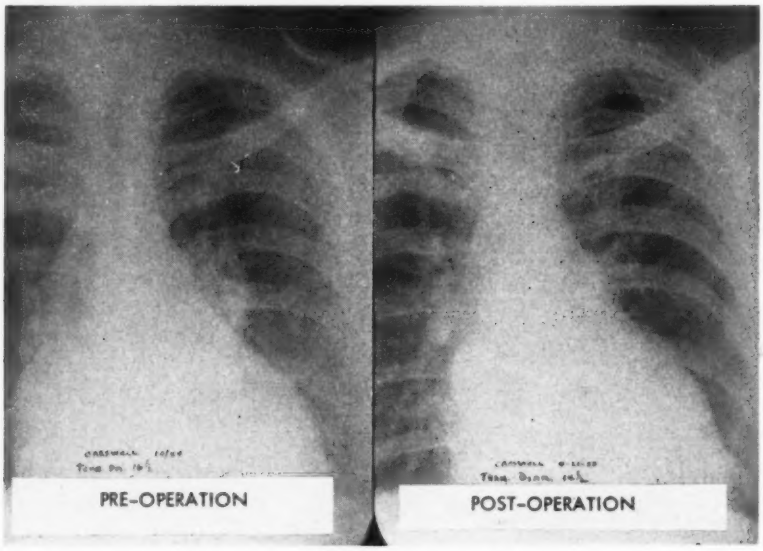

Fig. 3. Teleoroentgenograms before (October, 1954) and after (April 21, 1955) cardiopexy performed on November 16, 1954.

six-month to five-year period found a 13.1 per cent mortality rate as compared to an expected mortality rate of 30 per cent. Since the expected mortality rate in such a group as presented in our series is within the range of 35 to 50 per cent within an 18-month period,[3] 13 survivors out of 17 cases are gratifying.

It is illogical to attribute these results to mere coincidence. It must be concluded that the surgical procedure altered the course of the disease. Our clinical experience is supported by the laboratory evidence of surgical benefit as demonstrated by Beck and Leighninger.[4]

INTERNAL MAMMARY ARTERY LIGATION

In the second series, comprising 15 patients, internal mammary artery ligation was performed. This operation was deemed advisable for those patients whose clinical condition mitigated against cardiopexy or even general anesthesia. In May, 1957, Kitchell and Glover[5] reported successful relief of angina pectoris with internal mammary artery ligation. This opened a new potential avenue of surgical approach in these class IV patients. This procedure was unique in that surgery could be accomplished without general anesthesia and in addition avoided direct contact with the pericardium and the heart. Electrocardiographic changes therefore could not be attributed to the surgical manipulations and resulting pericarditis.

In March, 1957, we performed our first internal mammary ligation on a class IV patient, a 67-year-old female with severe hypertension and far advanced coronary disease. She had been under our care for the past three years. Medical therapy consisted of sedation, nitroglycerin, long-acting nitrates, digitalis, rauwolfia, and ganglionic-blocking agents. She was having constant chest pain, anginal in character, markedly exacerbated with any slight exertion, and frequent bouts of severe protracted coronary insufficiency. There was one definite and one suspicious infarction in the past. She had been considered for cardiopexy, but this was not offered to her since it was believed she would not tolerate a general anesthesia. On March 16, 1957, under local anesthesia, internal mammary ligation was performed. Three hours postoperatively this patient experienced a definite relief of a previously constant, dull, retrosternal distress. During the next five days there appeared to be a marked reduction of her angina. This subjective improvement was accompanied by objective evidence of improvement in her electrocardiogram. It is to be noted that this electrocardiographic improvement, which paralleled her clinical improvement, took place after a well established, fixed, severe coronary insufficiency pattern during a preoperative period of 15 months. The abrupt improvement in the ST and T changes occurring without change in therapy paralleled the diminished frequency and intensity of anginal pain.

This good result encouraged us to proceed with this type of surgery in 14 other extremely bad class IV risks. They ranged in age from 41 to 72 years. All 15 operations were done under local procaine infiltration anesthesia. The operative results were as follows:

TABLE III

Clinical Features of 15 Patients Subjected to Internal Mammary Ligation

Age range		41–72 years
Duration of symptoms		1–6 years
Previous infarctions		8
Transmural	6	
Subendocardial	2	
Hypertension		4
Cardiomegaly		6
Abnormal electrocardiograms		14

Excellent	3
Good	4
Fair	6
No improvement	1
Died	1

The operative death was in a 42-year-old male with definite infarction in the past. During the previous six months angina was progressive to the point of decubitus angina. Recent infarction was considered preoperatively in spite of stable electrocardiograms (which were markedly abnormal since the first infarction). Internal mammary artery ligation was performed with full realization that the prognosis was ominous. The patient succumbed

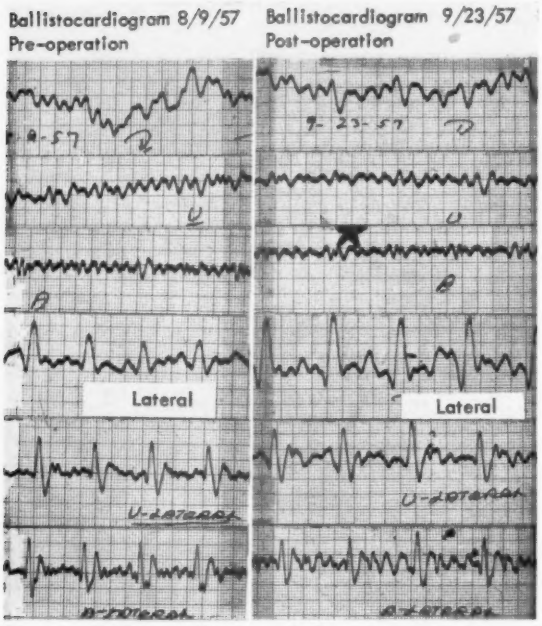

Fig. 4. Ballistocardiograms before and after internal mammary artery ligation performed on August 13, 1957.

within 24 hours. Autopsy revealed complete coronary inflow obstruction and an extensive fresh preoperative infarction.

Three of the four patients with pre- and postoperative electrocardiograms demonstrated objective ECG improvement. Two of the three cases with pre- and postoperative ballistocardiograms showed distinct BCG improvement postoperatively. It is of interest that in Glover's report of June, 1957, 60 per cent of his cases had either electrocardiographic or ballistocardiographic improvement. Figure 4 demonstrates the distinct ballistocardiographic improvement of one of our cases. The improvement is in the acceleration curves, which are the most diagnostic in coronary artery disease.

Some pertinent observations relative to this latter series occurred during surgery. Seven patients reported relief of angina immediately following ligation of the mammary arteries. In one instance a continuous electrocardiogram (cardioscope) demonstrated improvement of ST junction depression simultaneously with mammary artery ligation.

BECK I PROCEDURE

This procedure was performed on four cases with advanced symptomatic coronary artery disease. Because they were in a younger age group and did not present the complications of hypertension, cardiomegaly, or congestive failure, the Beck I procedure was deemed the operation of choice. To date, in the laboratory, the Beck I operation has produced the best results as measured by back flow studies and protection of survivors in experimental coronary occlusion in dogs.[4] Brofman's study[2] of survival comprised 137 patients who had the Beck I procedure, and his study revealed a lowered mortality rate than predicted for the natural course of the disease.

In our small series which comprised 4 male patients, 3 had excellent postoperative results and 1 died. The operative death occurred in a 42-year-old male. During surgery he developed ventricular fibrillation which responded to cardiac massage with reversion to sinus rhythm. Twenty-four hours postoperatively he died suddenly, either from ventricular fibrillation or cardiac arrest. Autopsy disclosed complete occlusion of both coronary vessels at their origin.

Discussion

The work of Beck[4] and Eckstein[6] and their co-workers amply demonstrates the increased myocardial blood flow with various surgical procedures and emphasizes that protection against death is afforded by this increased blood supply. They also showed a smaller infarction if the occlusion is preceded by one of the protective measures. These laboratory results can be readily transferred to our class III–IV cases in the cardiopexy group where we have 13 survivors, 11 of whom had good to excellent improvement.

The objective evidence of improvement in these cases is not striking in all instances. Some present marked electrocardiographic improvement, notably of the ST-T changes of severe ischemia to less abnormal ischemic patterns. Others present definite ballistocardiographic improvement. Some show reduction of cardiomegaly.

If the anginal state were truly corrected in the sense of an improved myocardial blood supply, then we could also expect some improvement in

functional capacity as measured by less fatigue or dyspnea on exertion, less nocturnal dyspnea, and amelioration of other signs of failure. It was remarkable that several of our cases totally disabled with dyspnea and angina did recover the ability to return to moderately strenuous work. The cardiac physiologist can readily demonstrate the hypodynamic action of the cardiac pump during an acute stage of coronary insufficiency, and this can be readily visualized in the patient with protracted coronary insufficiency who slips into failure and even acute pulmonary edema during his anginal state.

For the past decade medical skeptics have enjoyed free reign in their destructive criticisms of surgical procedures designed to relieve the cardiac cripple. In fact, this attitude has existed for many decades. Over 25 years ago the leading British cardiologist, Lord Mackenzie, successfully assaulted the concept of commissurotomy following its successful employment by Souter in the treatment of mitral stenosis. This stalemated this currently accepted and well documented surgical procedure for over 25 years. As recently as 1954, another internist in reviewing a series of patients with mitral commissurotomy, inferred that postoperative benefits were due to psychotherapeutic response to the scalpel. Today we know the fallacy of this reasoning.

Another recent criticism is that relief of angina following surgery is psychologic and in many instances due to decreased physical activity, since in the postoperative state the patient has an honorable excuse to limit his activities. Our experience belies this criticism. In our series each patient surviving surgery became more active. In fact, a major postoperative problem was discouraging excessive activity. In addition, in the mammary artery ligation group, we cannot help but be impressed by the fact that 7 of 15 patients experienced relief from angina within a short time following ligation of the vessels. All volunteered this latter information spontaneously shortly after surgery, since local anesthesia was employed.

In the cardiopexy series we were impressed with the fact that cardiac cripples in many instances were restored to useful activities. The subjective improvement of these patients cannot be ignored. We, as well as their referring physicians, were impressed by their marked increase in activities without pain, increase in cardiac functional capacity, and decreased need for cardiac medications, including digitalis in some instances.

Our experience, although brief, supports the merit of surgery as a form of treatment for severe coronary artery disease in selected cases.

Summary

(1) We have presented 36 cases of severe coronary artery disease treated by surgical procedures—cardiopexy, internal mammary artery ligation, and Beck I operation.

(2) Clinical improvement was noted in 30 of the 36 cases (83 per cent). Excellent results (complete or almost complete disappearance of angina) occurred in half the patients.

(3) Objective evidence of improvement as measured by the electrocardiograms and ballistocardiograms in several cases is presented.

(4) The internist and cardiologist should recognize that improvement may be offered by surgical technics in the treatment of coronary artery disease.

Addendum

Since this manuscript was submitted for publication the authors have had successful experience with 11 additional Beck I procedures.

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Review

Evaluation of the Transaminase Test*

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SINCE the report by LaDue *et al.*[1] on serum glutamic oxalacetic transaminase (SGO-T) in human acute myocardial infarction, numerous experimental and clinical studies have appeared. Although the enzyme was discovered in 1937 by Braunstein who referred to it as aminopherase,[2–4] and a practical method for its determination existed in 1951,[5–6] the relatively simple, accurate method of Karmen, Wroblewski, and LaDue[7] made possible the present widespread use of this enzyme test in the differential diagnosis of an ever-widening list of disease states. It is our purpose here to examine critically the evidence for the reliability and usefulness of this test.

The technic of the test and its status has been summarized by Conrad.[8] Many modifications have appeared[9–11] but most laboratories are still following the original method pretty closely and have found it satisfactory. It is well known that the enzyme is found in the blood and organs of animals,[12] of plants,[13] and bacteria.[14] In normal human organs, the concentrations of the enzyme are found in the following descending order: heart muscle, skeletal muscle, brain, liver, kidney, testis, lung, and spleen.[15] Heart muscle contains nearly twice as much per unit weight as liver and eight times as much as lung. The normal value in human serum has been established as ranging between 8 to 40 units[1] and is remarkably constant in health, varying only ±10 units irrespective of the ingestion of food, exercise, or other physiologic variations. Moreover, in stored refrigerated (0°–5° C) sera, the GO-T level in normal individuals remains unchanged for at least two weeks.

It has also been adequately demonstrated that many disease states do not alter the normal levels (Table I). These include allergic conditions, neoplasms (in the absence of liver metastases), inflammations, metabolic disorders, collagen diseases, degenerative diseases, and many miscellaneous conditions like anemia, ulcers, hypertension, congenital heart disease, congestive heart failure, digitalis, and old myocardial infarction.[8] Serum GO-T activity has not been found increased in any disease state unless there is concomitant acute damage to tissue with high GO-T content; i.e., heart muscle, skeletal muscle, liver, brain, kidney, pancreas, etc. The test has been found most useful in the detection of myocardial infarction[16] and hepatitis but is finding more and more applications both for positive diagnosis and for differential diagnosis by exclusion.

Experimental Background for Diagnosis of Myocardial Infarction

Since skeletal muscle trauma[17] will also elevate transaminase, it was necessary to find methods for producing myocardial infarction without introducing this factor. This has been achieved in several ways. In the first study of this kind, Agress *et al.*[18] injected plastic microspheres directly into the coronary arteries of 14 dogs by a nontraumatic, closed chest catheter technic.[19] As little as 5 per cent infarction of the heart caused significant SGO-T elevation.

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This study also demonstrated that the peak rise of SGO-T was roughly proportional to the size of the infarct. By another technic, Nydick *et al.*[20] placed ligatures on the coronary arteries after thoracotomy but left them untied until recovery of the animals, whereupon infarction was produced in nine animals by tightening the ligatures. Measurements on SGO-T directly following surgical manipulation were made on 19 dogs by Lemley-Stone[21] and Merrill.[22]

TABLE I

Chart of Transaminase Values in Disease

GO-T elevated	GO-T normal
Myocardial infarction, acute	Angina or coronary insufficiency
Myocarditis, acute	Rheumatic fever without carditis
Pericarditis, severe	Neoplastic disease without liver involvement
Pulmonary infarction, severe	Infectious diseases
Hepatocellular damage, active	Acute cholecystitis
Pancreatitis, acute	Perforated peptic ulcer
Hemolytic crisis	Arthritis
Crush injuries or burns	Metabolic disorders
Surgery	Allergic diseases
Gangrene	Dermatitis
Infarction of kidney, spleen, intestine	Anemias
Rapid cardiac arrhythmias	Intestinal obstruction
Muscular dystrophies	Acute renal shut-down
CNS disease	
Drugs—aspirin, codeine	

Further ligature studies have been recently reported by Losner,[23] who ligated the descending branch of the left anterior coronary artery below its bifurcation of the main artery in 12 dogs and considered this as "high ligation." In 10 other dogs, the descending ramus of the left anterior coronary artery was ligated and considered as "low ligation." Ten other dogs acted as sham operated controls. He found the mean SGO-T peak in the "high ligated" animals to be 382 units with a peak of 101 units for aldolase (control 16 units). In the "low ligated" animals, the SGO-T peak was 92 units and the aldolase peak was 59 units, with the control animals having SGO-T peaks of 71 units and aldolase peaks of 41 units. (Normal limits of aldolase range from 6 to 9 units in patients and 16 units in dogs.) Autopsy demonstrated the areas of necrosis in the "high ligated" animals to be greater than in the "low ligated" animals, with no necrosis in the control group. In these experiments, a definite relationship existed between the size of the infarct and the degree of SGO-T and aldolase elevations. A third method was the injection of virus III into the testicle of rabbits by Pearce and Preuss, a technic which will produce isolated myocardial lesions in some animals.[24]

By all of these methods, uncomplicated myocardial infarction has been accomplished in dogs and rabbits and the results compared to control animals. Serum glutamic oxalacetic transaminase was elevated whenever infarction occurred, and the degree of elevation was roughly proportional to the amount of muscle infarcted. Low elevations have occurred in control animals and have been variously attributed to the effect of anesthesia on the liver, pericarditis, etc. These do not alter the conclusion that as little as one gram of infarcted heart muscle will cause GO-T elevation. Moreover, it has been shown that tissue concentrations of enzyme disappear rapidly from infarcted muscle as opposed to normal uninfarcted muscle.[16,20,22]

Clinical Observations in Myocardial Infarction

The critical test for evaluating the reliability of the transaminase test for a firm diagnosis of myocardial infarction requires (1) significant elevation in the presence of minimal infarction of heart muscle: (2) exclusion of false positive reactions in angina or coronary insufficiency with or without equivocal electrocardiographic changes; (3) exclusion of diseases producing chest pain which can confuse the diagnosis of myocardial infarction, and (4) exclusion of other disease states which can also elevate transaminase levels.

Numerous articles have appeared on transaminase determinations in acute myocardial infarction. In all of these a positive diagnosis was made on the basis of a typical infarction pattern in the electrocardiogram, on a characteristic clinical picture, or both. It is apparent

TABLE II

Clinical Correlation of Acute Myocardial Infarction with SGO-T Elevations

Author and year	Number of cases proved clinically	SGO-T levels	
		Elevated	Normal or borderline
1955			
Steinberg[11]	24	22	2
Goldner[26]	10	10	0
Rudolph[34]	34	32	2
McHardy[35]	36	35	1
DuToit[39]	12	12	0
1956			
LaDue[25]	300	297	3
Kattus[27]	13	13	0
Chinsky[28]	116	108	8
Merrill[31]	9	9	0
Krause[32]	2	2	0
Denney[33]	66	63	3
Ostrow[36]	60	58	2
Biorck[37]	86	84	2
Kessler[43]	63	63	0
White[46]	24	12	12
1957			
Iversen[38]	51	50	1
Ratner[47]	64	59	5
Shabetai[40]	39	39	0
Hoevenaars[41]	33	33	0
Kattus[42]	111	111	0
Bing[44]	18	18	0
Kaltenbach[45]	10	10	0
Chinsky[29]	24	24	0
Losner[23]	15	15	0
Moore[48]	35	35	0
Total	1,255	1,214	41

Correlation: 96.9 per cent.

that complete accuracy assumes that no error existed in the interpretation of the electrocardiogram or clinical picture. In the proper use of the transaminase test it is necessary to obtain peak elevations usually by serial determinations in order to measure the range of the rise and fall in transaminase levels. In instances where only single or random tests are made, it is possible to miss the rise in level either because the determination is made before release of the enzyme from the infarcted area or too late in the development of the infarct when all the enzyme has been released. For this reason those cases which for one reason or another had only random determinations of transaminase without correlation with the expected time curve of this enzyme test have been eliminated.

Clinical Reports: LaDue *et al.*[16] considered the normal range of SGO-T to be between 10 and 40 units. They found the earliest rise to occur in 12 hours after myocardial infarction, with the average peak elevation in 24 hours and the level returning to normal in uncomplicated cases by the sixth day. Some authors have found elevations occurring as early as two hours or as late as 96 hours after infarction. Return to normal has varied between two and eight days.

Since the original reviews of LaDue *et al.*[25] in 1956 on data obtained from 300 patients with acute myocardial infarction, numerous other studies have appeared, and more are being published every month (Table II).

Steinberg and Ostrow[11] reported 24 cases proved by diagnostic electrocardiograms in which all but two showed elevations of SGO-T above 40 units. These two presumably false negatives were not discussed. Goldner and Meador[26] cited 10 proved cases (the eleventh was sampled five days after infarction) all of which were positive. Kattus *et al.*[27] observed only 1 negative reaction out of 14 patients. The one exception, however, died three hours after infarction. Chinsky *et al.*[28] reported 116 acute myocardial infarctions in 108 patients. There was positive ECG evidence in 84 cases; of these, 79 had elevated transaminase, 1 was borderline, and 4 were normal. Thirty-three were diagnosed as acute myocardial infarction without ECG evidence. Eight were subsequently proved by autopsy, and all but one who died one and one-half hours after infarction had elevated SGO-T's. Of the 25 remaining, 22 had high SGO-T's and 3 were borderline, although in these 3 cases samples were not taken at optimal times. Chinsky,[29] in a further report, discussed 24 cases of myocardial infarction all demonstrating an elevated SGO-T level. However, only 9 of these 24 developed elevated pyruvic levels with the GO-T rises being consistently higher. This is in accordance with the finding that the myocardium is 20 times richer in GO-T than in pyruvate.[30] Merrill *et al.*[31]

had 9 cases confirmed by high SGO-T levels. Krause *et al.*[32] reported 2 cases in which SGO-T established the diagnosis when the electrocardiographic pattern was obscured by the presence of left bundle branch block.

Denney and others[33] reported 77 cases of proved myocardial infarction in which 63 had elevated levels. However, of the 14 assumed to be false negatives only 3 cases had serial determinations, 5 were not sampled until after three days, and 6 were sampled only once. Eleven, therefore, do not meet the necessary criteria for analysis. Rudolph *et al.*[34] collected 39 cases of which 32 showed diagnostic elevations. Of the 7 "false negatives" only 2 had serial determinations, 1 died in three hours, and 4 were sampled after three days. McHardy *et al.*[35] found 35 out of 36 patients with acute myocardial infarction who had elevated SGO-T's.

Ostrow and associates[36] followed 60 patients with diagnostic ECG patterns of acute infarction. Of these, 58 showed elevated transaminase levels with peak levels ranging from 26 to 375 units in 2 to 96 hours. Biorck[37] had 2 false negatives out of 86 cases. Iversen *et al.*[38] reported 58 unequivocal acute myocardial infarctions with 50 SGO-T elevations. However, only 1 can be considered a false negative since the proper time relations were not observed in 7 cases. DuToit[39] had 12 cases followed carefully with positive elevations in all. Shabetai and co-workers[40] discussed 39 cases. Again all showed elevated titers of SGO-T. Hoevenaars and Overholt[41] also reported 33 cases of proved acute myocardial infarction with high transaminase levels in all. Kattus *et al.*,[42] in a further report on 111 patients with established diagnosis of acute infarction, found positive elevations in all. There were another 63 patients with elevated transaminase in whom the diagnosis could not be definitely proved. Seven of these died and at autopsy were found to have infarcts. Kessler[43] reported 63 cases of acute myocardial infarction, all of which had elevated transaminase levels. Of these 63, 8 died and upon autopsy all demonstrated areas of infarction. He also reported 32 cases with abnormal ECG, all with normal SGO-T levels. Bing[44] observed 18 acute cases with no false negatives or positives as did Kaltenbach[45] in his 10 reported cases. Bing[44] reported the activity of the enzymes malic dehydrogenase and isomerase as well as GO-T and found the levels of all three to be elevated in all cases studied.

White[46] reported 12 instances of false negatives utilizing the GO-T test in cases of recent myocardial infarction. One of these 12 cases was reported to have had a definite area of infarction at autopsy. These figures are at variance with other reports in that in no other instance was a positive autopsy finding of myocardial infarction not correlated with a definitive elevation in SGO-T levels, and in no other report were the false negatives found to be 50 per cent of the total number of cases studied. It is probable that the explanation for these findings lies in White's own statement, "that in many of these patients blood was not taken for enzyme analysis on the day after the attack, but several days later."

Ratner and Sacks[47] reported 64 cases of clinically proved myocardial infarction in which SGO-T was above 50 units in 59 cases, borderline in 1 case (43 units), and below 40 units in 4 cases. Of these 64 patients, 16 cases came to autopsy with elevations of SGO-T in all cases. In 40 cases of suspected (not proved) myocardial infarction, SGO-T was elevated in 31 (above 50 units), borderline in 5, and normal in 4. Four patients in this category who came to autopsy were found to have infarction, and in all SGO-T showed marked elevation.

Losner[23] reported 15 cases of acute myocardial infarction all demonstrating increased serum SGO-T and aldolase levels except for one case with normal aldolase levels. Losner also measured plasma fibrinogen, the C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR). He found the peak fibrinogen level appearing on the second or third day following coronary occlusion, with a return to normal at the end of the second or during the third week. The fibrinogen level never failed to rise in patients with unequivocal myocardial infarction but was primarily useful in reflecting the recovery stages. In comparison, the SGO-T and serum aldolase levels peaked within one to two days after onset and returned to normal three to four days later. Losner also states that although the ESR and CRP usually reach ab-

TABLE III
"Proved" Myocardial Infarction

Author and year	Number of autopsy cases		Autopsy evidence of infarction
	High SGO-T	Normal SGO-T	
1956			
Merrill[31]	1	0	1
Kattus[27]	3	0	3
Chinsky[28]	7	0	7
Ostrow[36]	11	0	11*
Biorck[37]	7	0	7
Kessler[42]	8	0	8
White[46]	0	1	1
1957			
Iversen[38]	5	0	5
Hoevenaars[41]	4	0	4
Ratner[47]	16	0	16
Total	62	1	63

* Ostrow—A total of 18 autopsies showing in addition to the 11 cases above: 2 cases clinically positive for myocardial infarction with normal SGO-T and no autopsy evidence; 2 cases clinically negative for myocardial infarction with elevated SGO-T and autopsy evidence; 3 cases with S-T and T electrocardiographic changes with negative clinical diagnosis for myocardial infarction and with SGO-T normal and no autopsy evidence.

normal values in acute coronary occlusion "they neither reflect the severity nor the duration of the disease." This investigator does not feel that SGO-T, serum aldolase, or fibrinogen levels alone can adequately reflect myocardial injury, but rather that they must be used together as a means of supplementing the electrocardiogram. Moore[48] reported 35 cases of myocardial infarction with abnormal values in all.

It is interesting to note that as one reviews the reports chronologically, the recent authors all pay proper attention to the necessary time curve of serum sampling, the number of false negatives greatly diminishes and in the last 8 reports completely disappears (Table II).

Thus to date, of 1,255 reported cases of acute myocardial infarction in which clinical and electrocardiographic evidence established the diagnosis and in which serial sampling was used to determine the SGO-T curve, all but 41 have exhibited titers elevated beyond the normal range, giving an over-all accuracy of 96.9 per cent (Table II).

Autopsy Reports: The ultimate court of appeal is autopsy proof of the presence or absence of infarction when the autopsy is performed in the proper time relationship to the occurrence of infarction. Of the 63 cases studied which have come to autopsy, all demonstrated myocardial infarction and in all but one the transaminase was significantly elevated, giving a positive correlation of over 98 per cent (Table III). Conversely, one author[36] has cited autopsy experience in which 2 cases were clinically positive for myocardial infarction with normal SGO-T and no autopsy evidence, 2 cases were clinically negative for myocardial infarction with elevated SGO-T and positive autopsy evidence; 3 cases with ST and T changes with a negative clinical diagnosis for myocardial infarction and with normal SGO-T levels and no autopsy evidence. Thus, in the 63 autopsies so far reported there was positive correlation in 62 cases and negative correlation in 1 case, or over 98 per cent agreement with the transaminase determinations.

Angina and Coronary Insufficiency

In the differential diagnosis of chest pain, there often exists the problem of the patient with ST and T wave changes in the electrocardiogram and with equivocal clinical and laboratory evidence of myocardial infarction. Here the worth of the SGO-T determination is of paramount interest.

Clinical Observations: LaDue and Wroblewski[16] originally reported 36 patients with angina or coronary insufficiency (Table IV). Of these, 21 had normal SGO-T levels and 15 were elevated. No proof of the presence or absence of infarction in these cases was available. Kattus *et al.*[27] reported 24 cases of which only 4 had SGO-T elevations over 40 units. None was higher than 57 units. Chinsky and co-workers,[28] in studying 69 cases, found 64 with normal SGO-T values and 5 with borderline levels of 41–50 units. Twelve of these, however, showed serial ranges within normal limits but greater than 20 units. Ostrow and associates[36] studied 18 cases with normal electrocardiograms. Six of these 18 were considered to be cases of angina and of

TABLE IV

Clinical Correlation of Acute Angina with SGO-T Elevations

Author and year	Number of cases	Transaminase			Peak elevations (units)
		Normal	Elevated	Equivocal	
1955					
LaDue[16]	36	21	15	0	—
1956					
Kattus[37]	24	20	4	0	57
Chinsky[38]	69	64	0	5	50
Ostrow[36]	6	4	2	0	80
White[46]	19	18	1	0	35
Denney[22]	2	2	0	0	—
1957					
Shabetai[40]	6	6	0	0	—
Hoevenaars[41]	30	30	0	0	—
Ratner[47]	33	28	1	4	Above 50
Moore[48]	10	10	0	0	—
Totals	235	203	23	9	

these 6 cases, 4 had SGO-T elevations. They also had 82 patients with only ST and T wave changes, some of whom were felt clinically to have infarction. In 16 cases, the clinical diagnosis and SGO-T value were in disagreement. It is interesting, however, to find that 5 of these 16 came to autopsy and in every instance the SGO-T diagnosis was correct in that no infarction was observed at autopsy when the SGO-T levels were normal.

Shabetai *et al.*[40] reported 6 cases of angina in which all had normal values of SGO-T. Hoevenaars *et al.*[41] observed 30 patients with severe angina but with absent infarction patterns in the ECG, normal white blood counts, sedimentation rates, and temperatures. All had normal transaminase titers. White[46] reported 19 cases of patients without myocardial infarction but with chest pain, arrhythmia, or both. In 1 case, the SGO-T was elevated (35 units) and in 2 cases the serum LDH, aldolase, and hexose isomerase were elevated.

Ratner and Sacks[47] reported 33 cases of angina with all but one having normal values and in 47 cases of coronary insufficiency only 5 were observed to have elevations in SGO-T levels. Losner[23] presented 15 cases with either subendocardial necrosis or coronary insufficiency in which the SGO-T levels never rose above 70 units and the aldolase levels above 13.5 units. Moore[48] found normal SGO-T levels in 10 cases of angina but elevated levels in 15 cases of coronary insufficiency.

Experimental Studies: Experimentally, coronary insufficiency has been produced in dogs by tightening ligatures around coronary arteries 10 days after the animal had recovered from the placement operation.[25] The ligatures were tightened until ST and T wave changes appeared in the electrocardiogram but without the appearance of Q waves. The coronary insufficiency experiments were extremely interesting in that 5 of the 26 dogs had increased SGO-T activity after tightening the suture. The electrocardiograms, however, were similar to those in the other 21 animals with normal SGO-T's. At autopsy all 5 of the dogs showing increased SGO-T activity had evidence of subendocardial infarct.

Autopsy Studies: It is evident that at the present time no definite statement can be made as to the reliability of the transaminase test in equivocal electrocardiographic and clinical situations. Autopsy proof is the only final judge and only a few autopsies are available. The five of these mentioned have bowed to the SGO-T test. Moreover, in 3 other instances where the ECG showed ST and T changes but the SGO-T was negative, the autopsies again supported the GO-T diagnosis. It would seem that a significantly elevated SGO-T curve which cannot be explained by other disease states should seriously suggest the diagnosis of myocardial infarction. It is likely, from the evidence so far available, that the equivocal cases with minimal transaminase rises now diagnosed as severe angina or coronary insufficiency in reality have small infarcts. It is important that all available autopsies in these situations be reported so as to be able one day to decide this question.

Pericarditis

It is often impossible to distinguish the clinical and electrocardiographic features of pericarditis from those of infarction, although the manage-

ment and outlook of the two conditions differ widely. LaDue *et al.*[25] studied 11 patients with clear-cut pericarditis (Table V). Two showed slight elevations of SGO-T which the authors thought might have been due to concomitant liver disease. The other 9 showed no elevation. Denney *et al.*[33] reported 5 cases, all with normal values. Chinsky *et al.*[28] also reported 5 cases of benign idiopathic pericarditis with normal values. The Kalmansohns[49] observed 2 cases of acute nonspecific pericarditis, one with a peak elevation of 75 units and one with 52 units. Kattus *et al.*[27] reported 4 cases with normal SGO-T titers. Ostrow *et al.*[36] included 4 cases with serial determinations and 3 with isolated determinations of SGO-T, all with normal values. In this group were patients with idiopathic and uremic pericarditis and metastases to the pericardium. Hoevenaars[41] collected another 5 cases of pericarditis; 4 had normal values and 1 with extensive tuberculous pericarditis had a SGO-T value of 48. Moore[48] found normal SGO-T levels in 1 case of pericarditis and so did White.[46] Thus, in 41 reported cases of pericarditis, SGO-T was normal in 36, elevated in 3, and equivocal in 2, the highest peak value being 75 units (Table V).

TABLE V

Clinical Correlation of Acute Pericarditis with SGO-T Elevations

Author and year	Number of cases	Transaminase		
		Normal	Elevated	Equivocal
956				
LaDue[25]	11	9	—	2
Denney[33]	5	5	—	—
Chinsky[28]	5	5	—	—
Kattus[27]	4	4	—	—
Ostrow[36]	7	7*	—	—
White[46]	1	1	—	—
1957				
Kalmansohn[49]	2	—	2‡	—
Hoevenaars[41]	5	4	1†	—
Moore[48]	1	1	—	—
Totals	41	36	3	2

All cases were benign idiopathic pericarditis except:
* Included uremic and metastatic pericarditis and
† extensive tuberculous pericarditis.
‡ Peak 75 and 52 units.

In an experimental study by Agress *et al.*,[50] pericarditis in dogs was produced by introduction of abrasive substances like talcum powder and of streptococci into the pericardial sac. It was found that the degree of elevation of the SGO-T level was related to the amount of subepicardial myocardial infarction produced rather than the extent of pericardial inflammation.

It may be concluded that, in general, SGO-T is elevated in only the severe forms of pericarditis. In the differential diagnosis of these cases of pericarditis which might be confused with myocardial infarction, a normal titer of SGO-T is strong evidence that the latter is absent.

Rheumatic Myocarditis

Several authors have reported on SGO-T values in rheumatic fever (Table VI). Nydick *et al.*[51] described normal values in rheumatic patients without clinical evidence of cardiac involvement. They found that although the SGO-T levels were frequently high in patients with active carditis, these elevations were not consistent and did not follow the clinical course of the disease, Manso *et al.*[52] obtained similar results in rheumatic children. The SGO-T sometimes rose as high as 540 and SGP-T to 900 units although the administration of aspirin lends considerable doubt to these values (see Drugs section). There was no correlation between enzyme activity and the sedimentation rate, WBC, C-reactive protein, the serum salicylate level or the use of cortisone. Chinsky[28] found a peak SGO-T level of 56 units in one rheumatic patient.

Pulmonary Embolism and Infarction

Pulmonary embolism with or without infarction of the lung often occurs after myocardial infarction as well as in many other conditions. Often the electrocardiographic changes and the clinical picture can be confused with myocardial infarction. Serum glutamic oxalacetic transaminase determinations may prove valuable in distinguishing these situations.

Experimental Studies: Experimentally, Agress

TABLE VI
SGO-T in Miscellaneous Conditions

	Author	Number of cases	SGO-T	
			Elevation	Peak values (units)
Rheumatic myocarditis	Nydick[51]	—	50%	—
	Chinsky[28]	1	1 with aspirin	56
	Manso[52]	—		540
Cardiac arrhythmias	Chinsky[28]	7	Rates 120–160/min.	14–38
		8	Rates above 180/min.	56–143*
	Chinsky[29]	1	1	72
Skeletal muscle				
Muscular dystrophy	Pearson[58]	87	54%	290
	Ritter[59]	4	—	236 peak
Dermatomyositis Polymyositis	Siekert[60]	52	Consistently elevated	—
Trauma	Lieberman[61]	51	47%	43–515
Pancreatitis	Denney[33]	10	50%	—
	Chinsky[28]	16	69% with jaundice	35–420
	Chinsky[29]	4	3	90
	Ratner[47]	2	2	Above 50
	Shabetai[40]	1	1	Very high
Infectious mononucleosis	Wroblewski[72]	10	0	—
Drug administration	Manso[52] (salicylates)	23	50%	50–146
	Foulk & Fleisher[79] (codeine)	16	38%	5–85 times control level†
Cardiac failure	Chinsky[28]	11	0‡	—
	Chinsky[29]	3	0	—
	Ratner[47]	5	0	—
	Lieberman[57]	14	3	45–420
	Denney[33]	9	0	—
	Kessler[43]	46	0	—

* 1 case of ventricular tachycardia of 250/min—750 units.
† Patients had abdominal pain, mostly postcholecystectomy.
‡ SGO-T values remained normal in presence of digitalis intoxication.

et al.[53] produced pulmonary infarction in dogs by injecting clots of the dog's own blood into the jugular vein after increasing the vascularity of the lung by preliminary administration of alpha naphthol thiourea. Serial sampling of SGO-T was performed from 2 to 40 hours after infarction after which autopsy showed 0 to 45 per cent infarction of the lungs. None of the animals showed elevations over 58 units and there was no statistical difference between infarcted and control animals. The slight rises were attributed to the toxic action of thiourea on the liver. Rudolph *et al.*,[54] on the other hand, found that ligation of major pulmonary vessels produced pulmonary infarction with peak values of SGO-T varying from 56 to 112 units.

These measurements were made in postoperative animals.

Clinical Observations: Clinically, LaDue *et al.*[25] followed 7 patients (Table VII). Six had normal levels but 1 had a peak value of 50 units. Denney *et al.*[33] reported 4 patients, 2 with normal values and 2 with elevated values. However, the latter were "probable" cases and not proved ones. Chinsky *et al.*[28] studied 2 patients with normal values. Goldstein *et al.*[55] studied 12 patients with pulmonary infarction. Eleven patients had normal SGO-T levels. The twelfth patient had a peak value of 78 units but was jaundiced.

Ostrow[36] collected 15 cases of pulmonary embolism. Of these, 8 had normal levels and 7 showed slight rises, the highest reaching 85 units. However, these rises did not occur until the fourth to sixth day and were usually accompanied by a rise in the icterus index suggesting that pulmonary infarction had ensued. Walsh *et al.*[56] in an unstated number of pulmonary infarctions concluded that while rises did occur in pulmonary infarction, they appeared usually after the fourth day and seldom rose above 100 units. However, rises did occur occasionally before the fourth day in the "myocardial infarction" zone. DuToit[39] found three cases with normal SGO-T values and 1 with a peak of 44 units. In Kessler's[43] three patients and in Ratner's[47] two patients, no elevations occurred (Table VII).

TABLE VII

SGO-T in Pulmonary Embolization

Author	Number of cases	Transaminase			Peaks (units)
		Normal	Elevated	Equivocal	
LaDue[25]	7	6	1	0	50
Denney[33]	4	2	2	0	—
Chinsky[28]	2	2	0	0	—
Goldstein[55]	12	11	1*	0	78
Ostrow[36]	15	8	7	0	85
Kessler[43]	3	3	0	0	—
DuToit[39]	4	3	1	0	44
Ratner[47]	2	2	0	0	—
Totals	49	37	12	0	

* With jaundice.

One must conclude that myocardial and pulmonary infarction cannot always be distinguished by the SGO-T curve, since of 49 cases 12 cases showed elevations. However, it can be said that pulmonary infarction usually does not elevate GO-T unless the infarctions are large (probably visible by x-ray), that the elevations are minimal and rarely over 75 units, that they tend to occur after the fourth day, and are usually accompanied by a rise in the icterus index.

Other Pulmonary Disorders: Of the miscellaneous pulmonary disorders, Chinsky *et al.*[28] reported that in 16 cases of pulmonary edema, 12 were normal, 3 were borderline and the only elevation of SGO-T occurred in a patient with rapid auricular fibrillation. Many authors agree that pulmonary edema and congestive heart failure do not elevate transaminase.

Cardiac Failure

Chinsky *et al.*[28] reported 11 cases with chronic congestive cardiac failure due to arteriosclerotic heart disease, all having normal SGO-T levels (Table VI). These levels remained unaltered in the presence of treatment for failure or in the presence of digitalis intoxication. A later report by these authors[29] included 3 other cases of congestive heart failure, none with SGO-T elevations, but with mildly elevated pyruvic transaminase levels.

Ratner and Sacks[47] found normal SGO-T levels in 5 cases of congestive failure. Lieberman[57] reported 14 cases with moderate to severe right heart failure with no evidence of myocardial infarction. Eleven of these had no elevations in SGO-T over 40 units. The 3 cases with rises had peaks ranging from 45 to 420 units. Denney[33] reported 7 cases of hypertensive heart disease with congestive failure and 2 cases of rheumatic heart disease with congestive failure all having normal SGO-T levels. Kessler[43] reported 46 cases of congestive heart failure all having normal levels of SGO-T.

Cardiac Arrhythmias

It has been an interesting observation that patients having very rapid arrhythmias have had elevations of SGO-T (Table VI). Chinsky *et al.*[28] reported on 14 patients with 15 episodes of arrhythmia. There were 7 patients with ven-

tricular rates between 120 and 160/min who had normal levels, and 8 instances of rates between 180 and 250 with peak levels ranging from 56 to 143 units with one determination rising to 750 units in a patient with a ventricular tachycardia of 250 beats/min. Autopsy on this patient did not reveal any disease of the myocardium, but he did have extensive liver cell necrosis of the centrilobular type, suggesting that this is the mechanism by which SGO-T is elevated. In other instances, autopsy has not been obtained and the possibility of subendocardial infarction has not been excluded. In Chinsky's normal patients where tachycardia was produced by strenuous exercise, no rise of SGO-T occurred. Chinsky[29] in a later report described another instance of rapid atrial fibrillation with an SGO-T level of 72 units.

Skeletal Muscle Disorders

Muscle Disease: Since skeletal muscle ranks next to heart muscle in enzyme activity, it would be expected that muscle disease and trauma would be associated with elevated SGO-T values (Table VI). Pearson[58] reported 87 cases of muscular dystrophy with elevations as high as 290 units in 47 (54 per cent). These levels may remain elevated for many months. One patient with dermatomyositis and one with paroxysmal myoglobinuria showed high levels. Cases of neuromuscular atrophy and myasthenia gravis exhibited normal values. Ritter *et al.*[59] observed 4 cases of pseudohypertrophic muscular dystrophy with high elevated SGO-T's and increased urinary coproporphyrins. The sustained levels suggested continued necrosis of skeletal muscle cells. One patient ran values as high as 236 units for over 3 weeks. Siekert and Fleisher[60] found consistently elevated levels in 52 cases of dermatomyositis, polymyositis, and dystrophy.

Muscle Trauma: Lieberman *et al.*[61] studied 51 patients involved in a variety of accidents. All had electrocardiograms and serial sampling of SGO-T. Of these, 72.5 per cent had elevated SGO-T levels and 17.7 per cent had evidence of myocardial damage. Elevations apparently unrelated to cardiac injury or surgical procedures occurred in 47.1 per cent. They concluded that the transaminase test was not a reliable one, therefore, to detect the presence of myocardial damage in accident victims.

Picktin[62] studied SGO-T levels in 12 patients in the presence of burns and fractures. In 2 patients with burns, 1 had 65 per cent of the body surface burned with a SGO-T peak of 322 units. The second patient had 25 per cent of the body surface burned with normal levels. In 10 fracture cases, 4 had severe muscle injury and all 4 had elevations up to 80 units. In the remaining 6, with minimum muscle involvement, 3 had normal levels and 3 had slight elevations of SGO-T.

Disorders of the Central Nervous System

Because the brain is rich in GO-T, cerebral infarctions or other destructive disease of the CNS might be expected to produce a rise in enzyme activity. It follows that the spinal fluid which bathes the brain and cord might reflect such brain changes (Table VIII). However, Fleisher and Wakim[63] demonstrated that only insignificant amounts of GO-T or GP-T were transferred from the serum to the cerebrospinal fluid following marked rises in the serum produced by administration of CCl_4 to dogs. Similar results were obtained by intravenous and intracisternal injections of massive concentrates of transaminases. The authors concluded that very little GO-T or GP-T passes the blood-brain barrier.

Miyazaki[64] also found that significant elevations of serum transaminase in disorders such as liver disease did not produce elevated cerebrospinal fluid GO-T levels. Therefore, it seems that elevated spinal fluid levels of GO-T or GP-T will not reflect systemic disorders. Miyazaki found control cerebrospinal fluid (CSF) GO-T levels to be 17 units/ml. He reported 20 cases with acute cerebrovascular accidents, 8 of which had cerebrospinal fluid GO-T elevations, 5 within the upper limits of normal, and 7 with no rise. However, the SGO-T levels were elevated during the first five days following onset in more than 50 per cent of the cases of acute cerebrovascular lesions. In 7 cases with proved or suspected brain tumors, only one showed a rise in the cerebrospinal fluid GO-T level and this was a case of suspected third ventricle tumor with internal hydrocephalus. Miyazaki also found that among miscellaneous

TABLE VIII

SGO-T in Diseases of Central Nervous System

Disease or Condition	Author	Subjects	GO-T Elevations		Peak time
			Serum	Spinal fluid	
Administration of CCl_4	Fleisher[63]	Dogs	High	Insignificant	2–3 days
Vinyl acetate injections	Wakim[65]	Dogs	110% increase	733% increase	4 days
		Humans			
Cerebrovascular accidents	Lieberman[70]	15	High or low	High or low	—
	Miyazaki[61]	20	Above 50%	8	—
	Green*[66]	11	—	All	17 days
	Fleisher[68]	21	9	6	—
	Myerson[69]	30	12	5	—
	Ratner[47]	3	0	Not done	—
	Lieberman[57]	21	9	Not done	Up to 6 weeks
	White[46]	2	0	Not done	—
	Green[67]	53	—	34 with 60% increase	3 days to 3 months
Brain tumor	Fleisher[68]	20	20	2	—
	Green[67]	14	0	Low	—
	Miyazaki[61]	7	—	1	—
Degenerative diseases	Fleisher[68]	25	5	9	—
Convulsive seizures	Fleisher[68]	19	4	5	—
	Green[67]	14	—	2	—

* Normal values on 15 patients: 2–7 units.

neurologic disorders only a few demonstrated elevated cerebrospinal fluid GO-T levels.

Wakim and Fleisher[65] by intracarotid artery injections of red vinyl acetate produced experimental cerebral infarction in dogs. The average increase in the spinal fluid activity was 733 per cent, while the serum increased 110 per cent. The peak levels were reached in approximately 100 hours. There was a rough correlation between the extent of cerebral damage and the spinal fluid GO-T levels but none between serum and spinal fluid levels.

Green *et al.*[66] reported 11 cases of cerebral infarction. One of these was proved by arteriography and 2 by autopsy. Myocardial infarction was excluded by negative electrocardiograms and none had evidence of liver disease. Normal spinal fluid values on 15 subjects ranged from 2 to 7 units, with an average of 5 units per milliliter. Seven of the 15 exhibited significant rises and all had elevated GO-T levels. The rises took place as early as the second day and tended to increase as long as 17 days (longer studies were not made). Green *et al.* in a later report[67] found the GO-T activity to be reduced when spinal fluid was stored at room temperature for over six hours but refrigeration for two weeks did not alter this activity. In this report, 53 cases of cerebral infarction were presented with 64 per cent having elevations representing an increase over the control levels of 60 per cent. These investigators found that thrombosis of the internal carotid artery produced the highest GO-T elevations, with middle cerebral artery occlusions yielding the lowest values. Of these 53 cases, there were 7 autopsies with proved cere-

bral infarctions in all and in 6 cases the cerebrospinal fluid GO-T was elevated, thus producing one false negative. Several cases in this series showed increasing levels of activity as long as 3 months after infarction, with high values not appearing until the third day. In cases with cerebral hemorrhage and clear spinal fluid the cerebrospinal fluid GO-T was found to be over two times the control level. In 14 cases of cerebral tumors, no GO-T elevations were observed and in 12 cases of multiple sclerosis, only 50 per cent showed increases. Also, in 12 out of 14 cases with convulsive disorders normal cerebrospinal fluid GO-T was found.

Fleisher *et al.*,[68] in a clinical study of 107 patients with cerebrovascular disease, head injury, degenerative diseases, and convulsive seizure, found GO-T and LDH elevations in both the spinal fluid and serum, with brain tumors only demonstrating a rise in the serum. It is interesting to note that brain tumors as a group caused a rise of transaminase only in the serum with few showing fluid rises. In 21 patients with cerebral infarction, the spinal fluid GO-T was increased in 6 and the serum GO-T in 9, with no correlation between the two. Lactic dehydrogenase (LDH) was increased in the one case that had bloody spinal fluid. Of 4 patients with cerebral contusion, the spinal fluid was high in 3 and the serum in 2 patients. Of 2 patients with subdural hematoma 1 showed an elevated fluid value, the serum remaining normal in both. There were 25 cases of degenerative disease of the CNS with increases in the fluid of 5 out of 19 patients with general or focal convulsive seizures, while the serum showed a rise in 4 patients.

Myerson *et al.*[69] found the normal cerebrospinal GO-T to average up to 20 units. In 3 cases with serum GO-T levels up to 1,000 units from hepatitis, the fluid levels were normal. In a wide variety of degenerative and convulsive diseases, primary and metastatic tumors, and miscellaneous diseases the values were largely normal but might be elevated in any group in either or both the spinal fluid and serum without any apparent relation between the severity of the disease or other findings. In 30 cerebrovascular accidents the same general conclusions held. Lieberman *et al.*[57] reported 21 patients with cerebral vascular accidents of which 9 were free of evidence of cardiac involvement. Serum GO-T levels were elevated in 57 per cent. In a further paper Lieberman[70] reported 15 patients with cerebrovascular accidents in which both blood serum and spinal fluid were tested for GO-T levels. He found that either or both spinal fluid and blood GO-T could be elevated. Lieberman also reported GO-T spinal fluid and serum elevations with brain surgery. In this report no relationship was found to exist between the serum and fluid GO-T activity. Also, Ratner[47] reported 3 cases of cerebrovascular accidents and White[46] 2 cases with neither observing rises in SGO-T.

In summary, it may be said that elevations of transaminase in the serum due to disease outside the CNS do not pass the blood-brain barrier to raise spinal fluid levels. However, diseases of the CNS do raise serum levels of transaminase as well as the level in spinal fluid, although there is no correlation between the two (Table VIII). A rise in the level of spinal fluid indicates some disease of the CNS but is entirely nonspecific. Moreover, almost any active disease of the CNS, including recent trauma or infarction, may exist with a normal fluid transaminase, although cerebral infarction is usually associated with a rise that persists for many days or weeks after the original injury.

Liver Disorders

Transaminase and Liver Cell Damage: In the original experiments of Molander, Wroblewski, and LaDue,[71] toxic injury to liver cells was produced by feeding rats CCl_4. By cardiac puncture blood was withdrawn for SGO-T, alkaline phosphatase, and cholinesterase determinations. Serum GO-T rose earlier and in greater amounts than the other enzymes and the rise was proportional to the amount of CCl_4 given and the extent of hepatic damage. They found that neither the serum cholinesterase nor alkaline phosphatase had the degree of sensitivity in reflecting hepatocellular injury as did the GO-T levels. In human toxic hepatitis due to drugs it was also found that SGO-T was elevated, falling to normal gradually when the toxic agent was withdrawn.[72] Friend *et al.*[73] showed that viral hepatitis in mice was ac-

companied by similar elevations of SGO-T being proportional to the degree of liver cell damage. Wroblewski and LaDue[74,75] further demonstrated in patients that marked rises in SGO-T occurred in hepatocellular damage due to poisoning with CCl_4 and in infectious hepatitis. These rises were much greater than those due to obstructions of the biliary tree. They also found that elevations occurred with cirrhosis and with metastases to the liver. In an institutional study of 151 patients exposed to hepatitis[74] (Table IX), the SGO-T test was shown to be important in picking up subclinical cases in which the transaminase elevation was the only indication of abnormal liver function one to four weeks before the liver injury was manifested. Preicteric rises of SGO-T during the use of chlorpromazine and other hepatotoxic drugs were also indicated. Furthermore, the test was useful in determining time of ambulation; when the GO-T returned to normal it was usually safe to allow activity of the patient even when other liver function tests were still abnormal. Ratner and Sacks[47] found SGO-T elevation in all 3 reported hepatitis cases with values as high as 900 units. Kessler[48] reported 3 cases with homologous serum hepatitis having GO-T levels from 80 to 468 units, with 1 case of toxic hepatitis having a peak of 698 units. Moore[48] found elevations in all 5 reported cases of infectious hepatitis.

SGP-T vs. SGO-T Levels: In a preliminary report by Wroblewski and LaDue[76] on pyruvic transaminase levels in liver disease, they found that normally GP-T was of a greater concentration in liver than in either heart or muscle as compared to GO-T, with normal SGP-T levels of 16 ± 9 units/ml/min. Because SGP-T levels did not increase significantly following myocardial infarction in 8 out of 9 cases it was thought that this enzyme might provide a more differential test for liver disorders than SGO-T. It was found that in acute infectious hepatitis and obstructive jaundice, the SGP-T levels were higher than the SGO-T levels, whereas in cirrhosis and in metastatic cancer of the liver the SGO-T levels were higher. Chinsky[29] has found that the pyruvic transaminase is not a more sensitive indicator than SGO-T in cases of hepatic necrosis, as both enzymes are elevated. However, he has found SGP-T values to be higher in viral hepatitis. Wroblewski and LaDue[30] have found SGP-T to be more sensitive than SGO-T in acute hepatocellular damage.

SGO-T and Phosphatase Levels: Shay and Siplet[77] in a study of chlorpromazine jaundice found that the SGO-T changes closely paralleled elevations in alkaline phosphatase. Furthermore, they found that SGO-T levels might rise sharply without any increase in serum bilirubin and at a time when very little if any parenchymal cell damage had occurred. They therefore questioned the view that the SGO-T rise in liver disease is indicative of death of liver cells and suggested that it might indicate merely an increased permeability of the cell to the hepatotoxic agent. The authors did feel that SGO-T was more sensitive than alkaline phosphatase in reflecting liver cell injury since phosphatase elevations indicated primarily obstructions of the biliary tree. Bing,[44] in studying the levels of malic dehydrogenase, isomerase, and SGO-T, found that highest levels of all three enzymes were found in hepatitis patients.

Mononucleosis with Hepatitis: Rennie and Wroblewski,[78] noting that the hepatitis of infectious mononucleosis is usually nonicteric and that the course is not well reflected by the usual liver function tests, studied 32 patients with this disease (Table IX). Serum GO-T and SGP-T were both followed, along with other liver function tests. All but two patients had increased SGO-T levels. Serum GO-T was less sensitive than SGP-T but both paralleled the clinical course of the disease. Wroblewski *et al.*[72] also found SGO-T elevations in all six cases reported to have hepatitis with infectious mononucleosis. However, 10 other cases with mononucleosis without hepatitis had no SGO-T elevation. Chinsky[28] found elevations in SGO-T from 50–150 units in 6 patients with hepatitis with infectious mononucleosis.

Liver Cirrhosis: Cirrhosis of the liver uncomplicated by hepatitis has lower elevations than infectious hepatitis. In Wroblewski and LaDue's 28 patients,[75] 8 had normal values, 14 had values ranging from 41–100 units, and 6 had values greater than 100. In their hepatitis patients the SGO-T activity varied from 500–2,500 units during the first week. In 2 cases of toxic hepatitis due to CCl_4, the values 48 hours after

TABLE IX
SGO-T in Liver Diseases

Disease	Author	Cases	SGO-T	
			Normal	Elevated range
Hepatitis	Wroblewski*[74]	151	—	Up to 27,800 units
	Ratner[47]	3	0	900 peak
	Molander[71]	20	0	540–1890
	Kessler[43]	4	0	80–698
	Chinsky[28]	5	0	Up to 1600
	Chinsky[29]	14	0	Elevated
	Bing[44]	2	0	460, 738
	White[46]	3	1	163, 169
	Moore[48]	5	0	—
Hepatitis with mononucleosis	Chinsky[28]	6	0	50–150
	Rennie[78]	32	2	—
	Wroblewski[72]	7	0	80–300
Chlorpromazine	Shay[77]	—	—	Elevated
	Bing[44]	1	0	65
Cirrhosis	Wroblewski[75]	28	8	41 to 100
	Chinsky[28]	13	5	Above 50
	Molander[71]	81	—	13–286
	Hoevenaars[41]	7	0	Elevated
	Kessler[43]	7	1	40–52
	Chinsky[29]	15	5	120 peak
	Bing[44]	7	1	46–114
	Moore[48]	7	0	Elevated
Extrahepatic jaundice	Wroblewski[72]	—	—	100–300
	Kessler[43]	4	—	70 peak
	Hoevenaars[41]	8	0	Below hepatitis
	Chinsky[28]	10	—	26–268
	Chinsky[29]	5	2	300 peak
	Molander[71]	1	0	320 peak
Liver metastasis	Wroblewski[72]	100	25	45–250
	Chinsky[28]	5	0	—
	Chinsky[29]	5	0	—
	Moore[48]	5	0	—

* 151 patients, including multiple forms of hepatitis.

exposure were 27,800 and 12,300 units, respectively. Chinsky *et al.*[28] on the other hand, reported on 14 patients with hepatitis with elevated SGO-T levels and 13 patients with Laennec's cirrhosis; of the 9 who were jaundiced 7 had high levels and 2 were normal. Of the 4 nonjaundiced patients only 1 had elevated values and this patient had a liver abscess and biliary cirrhosis. A later article by Chinsky[29] reports 5 cases of hepatitis, 4 of which had higher pyruvic transaminase values than SGO-T, but in 1 case the reverse was observed. Values up to 1,600 units were reported. This author also reports 15 cases of cirrhosis, 10 of which had high SGO-T levels and of these only 6 had high pyruvic levels. The SGO-T peaked at 120 units and the pyruvic at 60 units.

Molander[71] reported 81 patients with Laen-

nec's cirrhosis whose SGO-T levels ranged from 13 to 286 units. In 38 patients with compensated cirrhosis the range was from 13–150 units but in 43 with decompensated disease the range was from 28–286 units. In 7 patients with biliary cirrhosis the range was from 57–330 units. In 20 patients with viral hepatitis the range was between 540 and 1,890 units. No real difference existed between the levels in infectious and homologous serum jaundice. Hoevenaars[41] reported 7 cases of cirrhosis all showing elevations but he did not state the values. Bing[44] found the levels of malic dehydrogenase, isomerase and SGO-T generally elevated in cirrhosis and obstructive jaundice but to a lesser degree than in hepatitis. Kessler[43] reported 7 cases of cirrhosis with 6 having values ranging from 40–52 units. Moore[48] reported elevations in all 7 cases of Laennec's cirrhosis.

Differentiation of Intrahepatic and Extrahepatic Jaundice: In the differentiation of intrahepatic disease with jaundice and obstructive jaundice, SGO-T may again be helpful. Wroblewski, Jervis, and LaDue[72] stated that extrahepatic jaundice produced increments of SGO-T of from 100–300 units, and that the level falls to normal rapidly when the obstruction is relieved while alkaline phosphatase tends to remain elevated several days longer. Kessler[43] reported 4 cases, the highest reaching 70 units. Hoevenaars[41] gave no levels but stated that the values in 8 cases were lower than in hepatitis and remained elevated until removal of the obstruction. Molander *et al.*[71] cite one case of obstructive jaundice relieved by surgery in which the values fell from 320 to 27 units. Chinsky *et al.*[28] reported 10 cases in which the peak value ranged from 26–268 units.

Further work by this author[29] included five cases with extrahepatic obstructive jaundice secondary to lithiasis with three having elevated SGO-T levels (peak 300 units) and four having elevated pyruvic transaminase levels. The pyruvic range appears to be higher in this disorder than the SGO-T. Chinsky also reports four cases with intrahepatic obstruction secondary to thorazine with three of the four having high serum pyruvic transaminase levels (peak 220) and the fourth with a moderate pyruvic elevation. The SGO-T levels were moderately high (90 units) in three cases and normal in 1 case. Merrill *et al.*[31] found that in cases with common bile duct obstruction, although serum bilirubin might continue to rise, SGO-T stayed at a fairly constant level around 100 units. Moore[48] reports three cases of common bile duct obstruction with elevations in the SGO-T.

Hepatic Neoplasms: Wroblewski, Jervis, and LaDue[72] have also described SGO-T rises in 75 of 100 patients with primary hematoma or hepatic metastases ranging from 45 to 250 units. The enzyme activity was determined by the rate of growth and the size of the tumor tissue. They showed also that SGO-T is not elevated by bone metastasis, whereas either bone or liver metastasis may elevate alkaline phosphatase. Chinsky *et al.*[28] reported 10 cases of carcinomatosis, 5 with liver metastasis and elevated SGO-T levels, and 5 without liver metastasis and normal SGO-T levels. In a later article[29] these authors report 15 patients with metastatic malignancies, 5 of whom had proved hepatic metastases and of these 4 had high pyruvic and SGO-T levels and the fifth only an elevated SGO-T. In the remaining 10 cases hepatic metastases were not definitely proved and both pyruvic and SGO-T levels were found to be normal. Moore[48] reported 5 cases of metastatic cancer to the liver with elevated SGO-T levels in all cases.

Summary of Findings in Liver Disease: In liver disorders, therefore, SGO-T determined serially and with attention to the peak and to the time curve can be very useful in detecting hepatitis before icterus appears, evaluating the severity of the disease and determining when to ambulate the patient. It is valuable in distinguishing intrahepatic and extrahepatic jaundice and in detecting the presence of liver metastases.

Pancreatitis

Denney *et al.*[33] reported 10 cases of acute pancreatitis in which 5 showed elevations of SGO-T and 5 were normal (Table VI). Chinsky *et al.*[28] observed 16 cases in which 8 of 10 jaundiced patients had elevated values and 2 other jaundiced patients had borderline levels. In the nonjaundiced group, 3 were elevated, 1 borderline, and 2 normal. Values ranged

from 35 to 420 units. While the SGO-T values followed the serum bilirubin level there was no correlation with serum diastase. In a further study[29] 4 cases were reported with acute interstitial pancreatitis and biliary tract disease, all having serum amylase levels of more than 1,000 units/ml. Of the 4 cases 3 had elevations in pyruvic (90 units) and SGO-T (90 units) levels. Ratner and Sacks[47] also found elevations in their 2 reported pancreatitis cases as did Shabetai[40] in his one case.

Drugs

Manso *et al.*[52] investigated the effect of salicylates on the GO-T serum activities in 14 children, and SGO-T and SGP-T in 9 other children (Table VI). In 50 per cent of the cases there were elevations of both enzymes to abnormal levels. Serum GO-T elevations ranged from 50 to 146 units. Therefore, in active rheumatic carditis during salicylate administration the determination of SGO-T is of doubtful value.

Foulk and Fleisher[79] studied 16 cases with abdominal pain, mostly in postcholecystectomy patients where SGO-T samples were tested after administration of 2 gr of codeine phosphate by needle. Six of the patients showed rises in SGO-T levels up to 85 units. Serial determinations were not performed. All the patients with rises were postcholecystectomy patients where liver disease was not excluded. However, if this study is confirmed, caution must be exercised in the interpretation of the test after the administration of opiates.

Lactic Dehydrogenase

Wroblewski *et al.*[80] reported on lactic dehydrogenase in acute transmural myocardial infarction. This enzyme is also active in many tissues, in descending order: kidney, skeletal muscle, liver, heart, pancreas, spleen, brain, and lung. It is interesting to note that there are 240,000 units/g of LDH in wet heart tissue whereas 300,000 units/g of GO-T in wet heart tissue are present. These figures are representative of dog tissue.[17,79] In disease states, it was particularly elevated in leukemia, carcinomatosis, and myocardial infarction. In the latter, the serum level rose in 24 hours and returned to normal in 5–6 days. Wacker *et al.*[81] found LDH consistently elevated after myocardial infarction. Ruegsegger[82] *et al.* compared SGO-T and SLDH levels in dogs after experimental infarction and found SGO-T activity greater and elevated longer than the SLDH activity, with SGP-T levels remaining unchanged. White,[46] however, in 50 patients found SLDH far superior to SGO-T in diagnosis with regard to reliability and sensitivity. In fact, in the only statement of this kind in the literature he found SGO-T of "little clinical usefulness." He felt SLDH was superior chiefly because it remained elevated several days longer than SGO-T, aldolase, or hexose isomerase tests. His normal levels were around 90–100 units/0.01 ml. Kaltenbach *et al.*,[45] using a modified technic, found control levels of 22–39 units/min/ml. This group, in comparing SGO-T and SLDH levels in 10 cases of myocardial infarction, found peak SGO-T levels of 61–350 units and peak SLDH values of 55–162 units. The peaks of SLDH did occur later and reached normal values later than SGO-T.

An experimental study of particular interest is that of Jennings *et al.*[83] in which he points out that the loss of SGO-T in experimentally produced myocardial infarction in dogs begins after 40–70 minutes of ischemia, whereas SLDH begins to decrease 2 hours postligation and succinic dehydrogenase does not decrease in the infarcted papillary muscle until four to five hours postligation. MacDonald *et al.*[84] found the method of LDH assay much simpler than that of GO-T. In 40 normals, LDH varied from 165 to 332 units/ml serum. They found normal levels of SLDH in 13 patients with angina. In 44 patients diagnosed as myocardial infarction, values above 500 units were observed in 39. Maximal levels were obtained on the 2nd to 3rd days and reached normal by the 6th to 11th days. However, abnormal values were found in congestive failure, pericarditis, cerebral vascular accidents, diabetic acidosis, malignant diseases, hematological disorders, and various miscellaneous conditions.

Wroblewski[85] found in normal human tissue that 155,500 units of GO-T were present

per gram of wet heart tissue whereas 221,600 units of LDH were present per gram of tissue. In liver, skeletal muscle and serum the values, respectively, were: GO-T 142,400, LDH 94,700; GO-T 99,300, LDH 160,200; GO-T 20, LDH 470. Wroblewski, as did White,[46] also found SLDH activity to return to normal later than SGO-T activity, with peak elevations following myocardial infarction being two to fifteen times normal for SGO-T and 2–8 times for SLDH. It should also be pointed out in evaluating the relative merits of SGO-T and SLDH that red blood cells contain five times the GO-T activity of serum but one thousand times the LDH activity of serum. Consequently, slight hemolysis significantly increases LDH activity but affects SGO-T minimally.

Summary and Conclusions

(1) Serum glutamic oxalacetic transaminase (SGO-T) levels have been determined in 1,255 cases of acute myocardial infarction proved in the reports to date by a characteristic clinical picture and a diagnostic ECG pattern. In 1,214 or all but 41 cases the levels have exceeded the normal range, giving an accuracy of 96.9 per cent.

(2) In the 1,255 reported cases, 63 have come to autopsy. All but one had significantly elevated SGO-T determinations and all showed tissue evidence of acute infarction. In an additional 4 cases with normal SGO-T values but with electrocardiographic evidence of myocardial infarction, autopsy showed no infarction. Thus the correlation of SGO-T level with autopsy evidence has so far been over 98 per cent.

(3) In the cases diagnosed as angina, it is at present impossible to state the accuracy of the SGO-T test since only autopsy will settle the problem. However, 5 of these disputed cases, in which the clinical and SGO-T data were in disagreement, have come to autopsy and in all 5 autopsy has supported the SGO-T diagnosis. Experimentally also, SGO-T has been found reliable in distinguishing ischemia from infarction.

(4) Serum GO-T determinations have proved valuable in detecting active myocarditis, chiefly in rheumatic fever patients.

(5) In the differentiation of pericarditis from myocardial infarction, in 41 reported cases of acute pericarditis SGO-T was normal in 36 and elevated in 3, the highest peak value being 75 units. From clinical and experimental data it seems that SGO-T is elevated only in severe pericarditis where there is subepicardial myocardial necrosis. A normal SGO-T titer is strong evidence that myocardial infarction is absent.

(6) Of 49 cases of pulmonary embolism 12 showed elevated SGO-T levels. But important distinguishing features from myocardial infarction are: the elevations with pulmonary infarction are minimal (rarely over 85 units), they tend to occur after the 3rd day, and they are usually accompanied by a rise in the icteric index and the appearance of a shadow in the chest x-ray.

(7) Serum GO-T may be significantly elevated in the presence of sustained cardiac arrhythmias when the rate exceeds 180/min.

(8) There are various skeletal muscle disorders which may elevate SGO-T. These include trauma, muscular dystrophies where the values may remain high for months, dermatomyositis, myoglobinuria, polymyositis, etc.

(9) In disorders of the central nervous system it has been found that conditions which elevate GO-T in the serum do not pass the blood-brain barrier and that, therefore, elevated GO-T levels in the spinal fluid reflect only diseases in the CNS itself. On the other hand, disease of the CNS producing cerebral infarction may elevate the level of GO-T in in the serum, sometimes for many days, as well as the level in the spinal fluid, although there is no correlation between the two.

(10) In diseases of the liver SGO-T has been shown to be a sensitive test. It is useful in detecting hepatitis of all types before icterus appears, as in viral hepatitis of infectious mononucleosis, or in chlorpromazine sensitivity; in determining the severity and course of the disease, and in deciding when ambulation is safe from the danger of relapse. It is valuable in distinguishing intrahepatic and extrahepatic jaundice, since in the latter the peak determinations rarely exceed 300 units whereas elevations in intrahepatic diseases such as hepatitis often

reach very high levels. Serum GO-T elevations are often useful in detecting the presence of liver metastases particularly when bone metastases exist, since SGO-T is not elevated by the latter.

(11) Acute pancreatitis is another disease which frequently elevates SGO-T levels. Certain drugs as aspirin and codeine but not digitalis may cause a rise in SGO-T. There are other miscellaneous conditions which also elevate SGO-T as well as many that definitely do not (see Tables I and VI). It is important to be aware of these situations in the interpretation of the test.

(12) Other enzyme tests are now being studied. Lactic dehydrogenase (LDH) is useful in the diagnosis of myocardial infarction in those cases where several days have elapsed from the onset, since it often remains elevated several days longer than SGO-T. Pyruvic transaminase (GP-T) is helpful in distinguishing myocardial from liver injury, since it is more sensitive to liver cell injury than to myocardial infarction.

(13) The serum SGO-T values remain normal in the presence of cardiac failure. Of 98 reported cases only 3 had elevations.

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Experimental Studies

Dietary Production of Myocardial Infarction in Rats

Anatomic Features of the Disease*

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VASCULAR damage has been produced in thousands of experimental animals but the study of one of the principal fatal complications of this disease in man has been hampered by the lack of a method for producing coronary thrombosis and myocardial infarction in an experimental animal.[1] In the course of experiments previously reported we demonstrated that certain saturated fats, when administered orally, decreased the rate of lysis of blood clots.[2,3] It has been demonstrated by others that certain fats increase the coagulability of blood.[4] Therefore, we performed an experiment in which rats were given a known atherogenic diet high in cholesterol[5] altered to contain large amounts of saturated fats that had been demonstrated to increase coagulability and to decrease the fibrinolytic activity of blood. We reasoned that if the cholesterol-induced arteriosclerosis could provide a *local* factor favoring thrombosis, a suppression of the fibrinolytic system and an increase in coagulability of the blood might provide a *systemic* factor allowing small mural thrombi that might form on the plaques to build up into large occlusive thrombi.

The results of our first experiment, already reported,[6,7] far exceeded expectations. Myocardial and renal infarcts occurred in a large percentage of the rats.

The purpose of the present report is to describe the general anatomic features of the disease thus produced in rats and to provide confirmation of the original results by data from two subsequent experiments. Although many variations in diet have been tried in small groups and infarcts resulted, one diet (see Table I) was selected and given to a large

TABLE I

Ingredients in Diet (Per cent by Weight)

Casein	20.0
Sucrose	20.7
Butter	40.0
Cholesterol	5.0
Sodium cholate*	2.0
Thiouracil	0.3
Celluflour	5.0
Salt mix**	4.0
Vitamin mixture†	2.0
Choline chloride‡	1.0

* In one experiment bile salts were substituted for sodium cholate.

** This salt mixture is the Wesson modification of Osborne and Mendel salt mixture (*Science* 75: 339, 1932).

† Each kilogram of the vitamin mixture contained the following triturated in dextrose: Vitamin A concentrate, 4.5 g (200,000 units/g); vitamin D concentrate, 0.25 g (400,000 units/g); alpha tocopherol, 5.0 g; ascorbic acid, 45.0 g; inositol, 5.0 g; menadione, 2.25 g; P aminobenzoic acid, 5.0 g; niacin, 4.5 g; riboflavin, 1.0 g; pyridoxine hydrochloride, 1.0 g; thiamine hydrochloride, 1.0 g; calcium pantothenate, 3.0 g; biotin, 0.02 g.; folic acid 0.09 g.

‡ In one experiment 1.0 per cent choline chloride was given but in the next 0.2 per cent.

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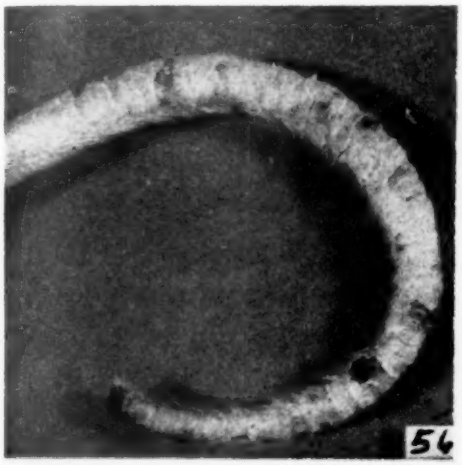
number of rats to establish better the incidence of infarcts and to provide abundant material for anatomic study. Although anatomic features have been similar in all rats thus far studied, the current report is limited principally to the large group of rats on one diet. Results from rats given other diets will be reported subsequently.

Materials and Methods

Fifty male albino rats of the Wistar strain (25 in each of two consecutive experiments), initially weighing 100 g, were housed in individual wire-bottom cages in an air conditioned animal room. They were weighed weekly. Water and food were given *ad libitum* and a daily record of food intake kept. The diet is presented in Table I. Animals dying during the course of the experiment were refrigerated until autopsied, and those surviving eighteen weeks were killed and autopsied. Blood was obtained by decapitation in one experiment and by clipping the tail in the next experiment and the total plasma cholesterol content determined by the method of Pearson, Stern and McGavack.[8] Autopsies were performed and microsections of major organs were



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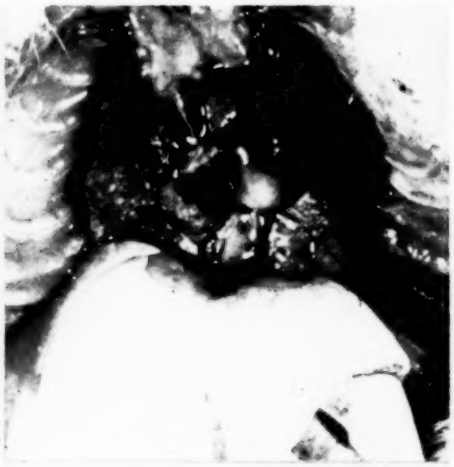

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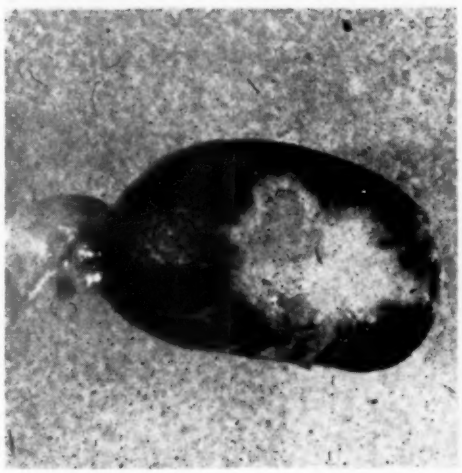

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Fig. 1. The scaly and superficially ulcerated tail of one of the rats. The end of the tail has been clipped to obtain blood for cholesterol determinations.

Fig. 2. Gross photograph of a small apical cardiac infarct, appearing as a pale area in the center of the picture. The liver appears extremely pale due to the large amount of fat present. Five-sixths of actual size.

Fig. 3. Gross photograph of a large renal infarct involving about one-third of a kidney. The pale surface of the infarct is depressed. At one pole of the kidney is the adrenal. × $2^1/_2$.

Fig. 4. A large recent infarct of the kidney with well-defined margins. The central area of infarction is pale. Hematoxylin and eosin. × $16^2/_3$.

prepared from carbowax-embedded tissue and stained with aldehyde-fuchsin–van Gieson–iron hematoxylin and with Oil Red O to demonstrate lipid.[9] On selected blocks, containing infarcted tissue, serial sections were performed in order to search for thrombi.

Results

Results are summarized in Table II. The rats in both experiments failed to gain weight. Their fur became dull and matted but there was no loss of hair. Tails were usually scaly, sometimes containing small crusted areas (Fig. 1). The rats were docile, relatively inactive and moderately emaciated.

Cardiovascular System and Kidneys: The most striking finding at autopsy was the presence of infarcts, approximately equally common in the hearts and kidneys (Table II). The infarcts varied in size from those involving almost the entire left ventricular wall or one-third of a kidney to small 2 mm areas of apical scarring in hearts or small focal depressions of renal cortex (Fig. 2 and 3). Microscopically, many of the infarcts had the typical "ghost-like" necrosis centrally and an infiltrate of chronic inflammatory cells and fibrosis peripherally (Fig. 4). Prominent accumulations of fat were present in myocardial infarcts and around renal infarcts. Very recent infarcts outlined by a zone of hyperemia were not commonly found, and infarcts of other organs have not been seen.

Mural endocardial thrombi commonly over-

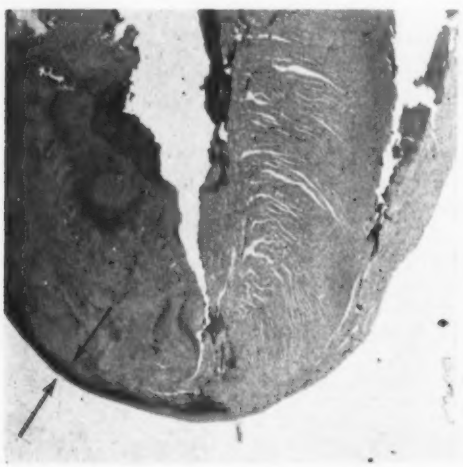
TABLE II

Plasma Cholesterol Content, Percentage Survival and Incidence of Infarcts in the 50 Rats Fed the Diet Listed in Table I

Group*	I	II
Number of rats	25	25
Total plasma cholesterol (mg %)**	410 (3)	1910 (21)
Survivors at 4 months	48%	0%
Number with cardiac infarcts	6	5
Number with renal infarcts	5	4
Number with either cardiac or renal infarcts or both	8 (32%)	7 (28%)

* The group designation refers only to the sequence of the experiments, which were conducted in the summer (I) and winter (II), respectively.

** The numbers in parentheses refer to the number of rats on which cholesterol determinations were performed, in Group I at the end of the experiment at 150 days and in Group II on the tail blood at 35 days. Determinations were repeated on the three remaining rats in Group II at 102 days and averaged 3064 mg %.



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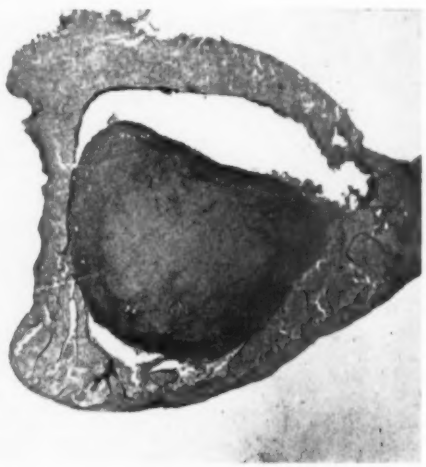

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Fig. 5. Low power photomicrograph of a large myocardial infarct. The remaining left ventricular wall is markedly thinned and seen only as a very narrow band to the bottom left (arrows) outlined in black due to the large content of fat. Overlying the endocardium is a large mural thrombus which is as thick as the interventricular septum. The right ventricular cavity is seen in the upper right. Oil Red O–hematoxylin. × 10.

Fig. 6. A large thrombus almost fills the left atrium. The thrombus is beginning to organize at several points along its attachment. Aldehyde fuchsin–van Gieson. × 17½.

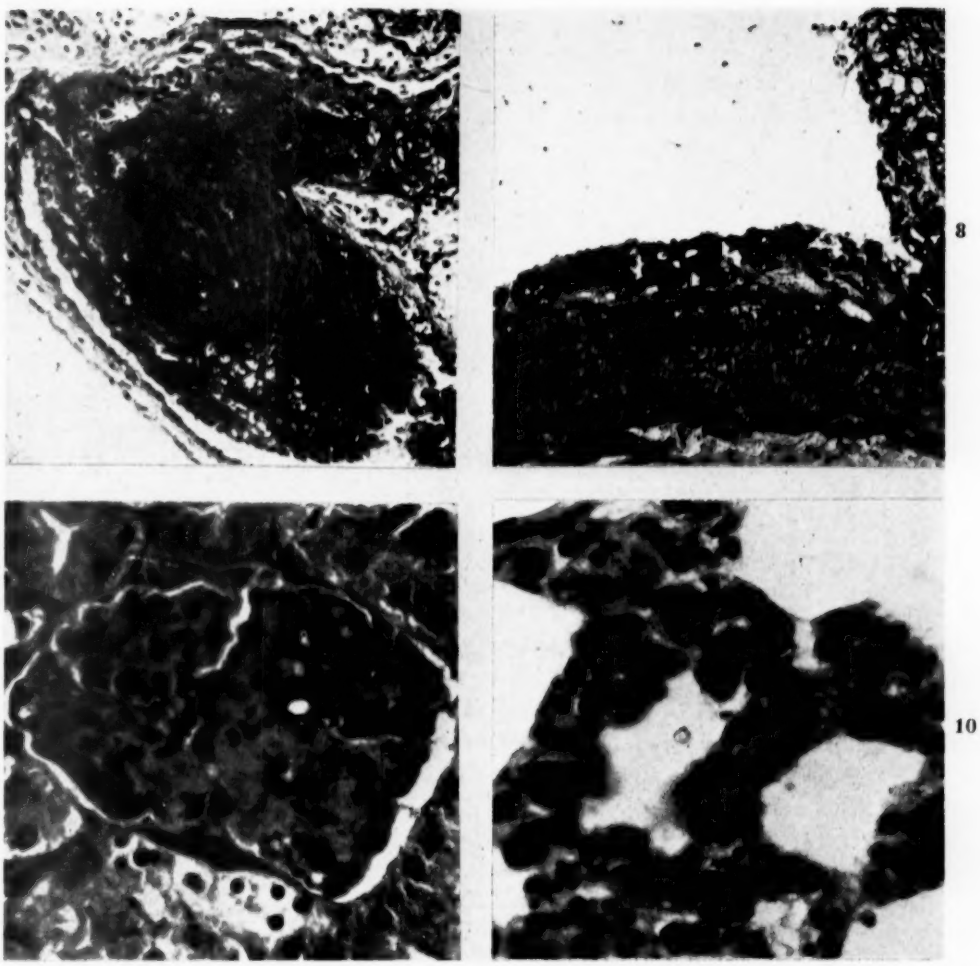


Fig. 7. A thrombus lying at the bifurcation of a small artery. At the lower left the surface of the thrombus is endothelialized and a slit-like vascular lumen is present. The fine black particles in the thrombus are fat. Oil red O–hematoxylin. × 166.

Fig. 8. Intimal collections of lipid laden "foam" cells, appearing black, at the ostium of a coronary artery. In many vessels of all organs there were fine fat droplets scattered through the walls even in the absence of intimal change. Oil red O–hematoxylin. × 133.

Fig. 9. A renal glomerulus. The capillaries contain large fat globules which appear solid black. Oil red O–hematoxylin. × 625.

Fig. 10. The capillaries in the alveolar walls are filled and markedly distended with fat, appearing solid black. Oil red O–hematoxylin. × 625.

laid cardiac infarcts (Fig. 5), and one was found in an atrium which was not infarcted (Fig. 6). Organizing thrombi, in arteries corresponding to the locations of infarcts, were demonstrated in some; because of the size of the arteries they were never seen grossly. Rarely, thrombi were found in animals without infarcts (Fig. 7). Large amounts of stainable fat were present in the thrombi.

The aortas never contained grossly visible intimal lesions, but one of the earliest gross changes noted was the presence of small yellow endocardial plaques about the aortic and mitral valve rings, appearing as early as one month. Occasionally, such a plaque (cholesterol-induced atheroma) was present at the orifice of a coronary artery (Fig. 8). However, these atheromata were never found underlying occlusive thrombi.

The commonest lesion demonstrated in blood vessels was the presence of fine lipid droplets focally and diffusely dispersed through walls of aortas and arteries of all organs.

Other Kidney Lesions: In addition to the previously described infarcts, the kidneys were the site of several interesting lesions. Two of the nine rats in the last experiment that survived for three months had small 3 mm stones in one or both renal pelves. Foci of calcification were also occasionally seen microscopically beneath the renal pelvic epithelium and near the corticomedullary junction.

The basic glomerular structure was intact but in practically every rat large fat globules were present in glomerular capillaries, appearing to fill and distend the capillary lumens. In some animals practically every capillary of every glomerulus contained fat (Fig. 9).

Lungs: The pulmonary alveolar capillaries were also filled with large amounts of fat, which produced an appearance of widening of alveolar walls (Fig. 10). Lipid-filled alveolar macrophages were often present in large amounts in air spaces.

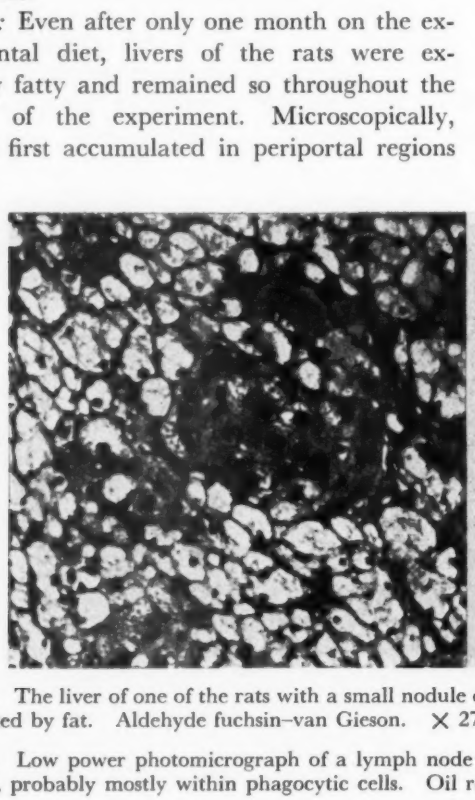
Liver: Even after only one month on the experimental diet, livers of the rats were extremely fatty and remained so throughout the period of the experiment. Microscopically, the fat first accumulated in periportal regions but later all areas were affected. The individual cells were extremely distended with fat. Later the livers became finely nodular by gross inspection and definite nodules of regeneration appeared microscopically, characteristic of early cirrhosis (Fig. 11).

Spleen and Lymph Nodes: With the appearance of fat in the liver, the splenic sinusoids and those of lymph nodes became packed with fat which appeared to be within phagocytic cells (Fig. 12).

Endocrine Organs: As would be expected with thiouracil feeding, the thyroid glands were enlarged (average weight 75 mg) even when compared to thyroid weights (average 42 mg) of adult controls with body weights four times greater. Microscopically the thyroid acini were small, contained very little colloid and were lined by columnar cells.

The adrenals grossly were extremely yellow like the livers, and microscopically the adrenal cortical cells were greatly distended with fat. The first zone affected was the fasciculata, and later there was sometimes marked atrophy of the fascicular zone with disappearance of cortical cells in this area.

The testes were small and microscopically few or no sperm were seen, maturation of spermatogenic cells being arrested. Increased numbers of lipid droplets were present in the



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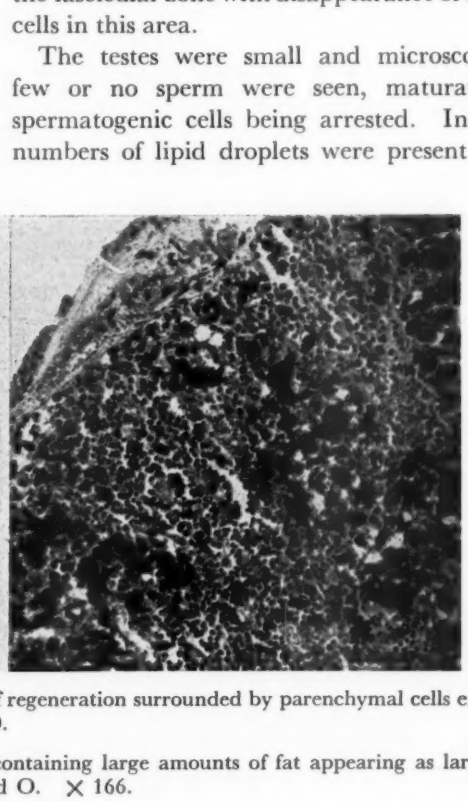

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Fig. 11. The liver of one of the rats with a small nodule of regeneration surrounded by parenchymal cells extremely vacuolated by fat. Aldehyde fuchsin–van Gieson. × 270.

Fig. 12. Low power photomicrograph of a lymph node containing large amounts of fat appearing as large black droplets, probably mostly within phagocytic cells. Oil red O. × 166.

undifferentiated cells of the basal layer of tubular epithelium.

Discussion

Myocardial and renal infarcts occurred in a large percentage of rats fed a diet high in saturated fats plus substances known to produce atheromata in rats: cholesterol, thiouracil and bile salts or derivatives. Results of a series of three experiments, one reported previously and two reported herein, indicate this is a reliable method for the experimental production of infarcts.

These experiments were originally designed to produce atheromata with overlying thromboses, but occlusive thrombosis occurred in arteries with only fine lipid droplets dispersed within their walls, prior to the development of significant atheromata. Apparently, lipid infiltration of arterial walls demonstrated in these animals provides a *local* factor sufficient to initiate the formation of a thrombus. Since other investigators have studied cholesterol-induced lesions in thousands of experimental animals and found only a rare infarct, it appears that the addition of a large percentage of saturated fats to the diet provides a general or *hematologic* factor favoring thrombosis and/or interfering with fibrinolysis. Our previous work has shown that oral feedings of saturated fats do interfere with the normal fibrinolytic system in rabbits,[2,3] and others have shown an increased coagulability of blood following fatty meals in man.[4]

In a previous report we have pointed out that substitution of fats other than butter in the experimental diet also results in the production of infarcts. If a specific factor in the diet is responsible for thrombosis, butter is not its only source.

Arterial thromboses with infarction were the most striking anatomic features of the dietary disease produced in these rats, but other lesions were prominent. Lipid globules in large numbers were present in the capillaries of the renal glomeruli and pulmonary alveolar walls, indicating that such large fat droplets were present in the circulating blood during life. Reticuloendothelial cells of the spleen and lymph nodes were filled with lipid. An extreme accumulation of fat occurred in hepatic parenchymal cells and even the adrenal cortical cells were distended with stainable fat. These accumulations of lipid may be simply the result of the tremendous dietary intake of fat, although supplement of even 1 per cent choline will not prevent them.

Lipid appeared in the thrombi in large amounts, suggesting an affinity between fibrin and lipids in the blood. We have previously demonstrated this affinity in rabbits fed butter and cholesterol.[10] These rabbits were injected intravenously with blood clots and large amounts of stainable fat appeared in the thrombi lodged in small pulmonary arteries. The physical affinity between fat and thrombi is striking and is possibly related to the formation of occlusive thromboses in the present experiment. However, more experiments must be performed before the specific mechanism responsible for the production of thromboses is understood and the significance for man determined.

Summary

Arterial thromboses with myocardial and renal infarcts occur in a large percentage of rats fed a known atherogenic diet to which is added large amounts of saturated fats. Thromboses occur before the formation of significant local intimal lesions, indicating that some hematologic factor is involved. The mechanism of formation of the thrombi is unknown.

The altered state produced in these animals is also characterized by marked accumulations of fat in the liver, spleen, lymph nodes and adrenal cortex as well as the presence of large fat globules lodged in the capillaries of the lungs and renal glomeruli.

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Seminar on Ballistocardiography

Guest Editor

SIDNEY R. ARBEIT

The Role of the Ballistocardiograph in the Diagnosis and Management of Patients with Coronary Heart Disease

Stress Tests and the Cigarette Test*

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THE PAST 18 years have seen the growth of ballistocardiography and the widespread utilization of this instrument in the clinic. The hope has been often expressed that ballistocardiography might prove to be a technic for the study of certain cardiovascular phenomena which have not been readily accessible through other avenues of study. Foremost in the thoughts of many investigators has been the potential value of the ballistocardiograph in the detection of coronary artery atherosclerosis. It is the purpose of this presentation to offer a brief summary of the current thoughts of a group† whose interests are primarily directed toward a more basic understanding of the physical and physiologic fundamentals underlying the ballistocardiogram and secondarily toward the clinical usefulness of the discipline or technic. No effort will be made to review the available literature, since this has been done elsewhere.[1,2]

The very considerable need for an objective means of appraising the coronary circulation in the intact human is widely recognized. At the present time, insufficiency of coronary flow is judged largely by the clinician's interpretation of subjective symptoms as expressed by the patient. The multitude of laboratory methods which have been used in efforts to objectify the presence of impaired coronary flow attests the inadequacy of any one of them. With the specific exception of the electrocardiographic pattern of myocardial ischemia, no laboratory method is available which permits the physician confidently to diagnose coronary insufficiency or occlusion. Moreover, the detection of latent coronary disease in the apparently normal subject is fraught with even greater difficulty.

THE RESTING BALLISTOCARDIOGRAM AND ELECTROCARDIOGRAM

Resting Electrocardiogram in Coronary Disease: The usefulness of the electrocardiogram in determining the presence of myocardial infarction, especially acute infarction, is well known and need not be reviewed here. Pathologic study and surgical observation have clearly indicated that infarction may occur in the absence of specific electrocardiographic patterns. However, the frequency with which the ECG fails to show *some* alteration at *some* time in the course of an infarction must be relatively low. On the other hand, its usefulness in the retrospective approach is considerably less. Our experience indicates that less than 70 per cent of surviving patients, examined months or years after a clinically substantiated infarct, have

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abnormal electrocardiographic patterns and many of these are not definitely diagnostic.[1] In a large group of patients whose clinical features were felt to justify the diagnosis of angina pectoris, an even lower incidence of abnormal tracings was found (24 per cent).[1] Of the one in four patients with historical evidence of angina pectoris whose ECG is abnormal, few show patterns which can be considered as diagnostic of this condition and most show abnormalities which are "nonspecific," i.e., that may occur in conditions other than coronary disease.

Resting Ballistocardiogram in Coronary Disease: It has been the hope of ballistocardiographers that they could offer a method which, because of greater sensitivity to myocardial (or vascular) abnormalities, might facilitate the early detection of coronary insufficiency. Despite some claims to the contrary, no broad usefulness in this direction has evolved with presently available ballistocardiographic technics. The incidence of abnormal BCGs in patients with angina pectoris or remote myocardial infarction is about 75 per cent.[1] Two limitations of this method are clearly apparent. First, there is definite correlation of ballistic abnormality with age, so that although almost without exception patients with coronary heart disease over the age of 70 show abnormal tracings, less than 50 per cent of those under 40 show deviation from normal. Second, the high incidence of abnormality of ballistocardiographic pattern in clinically normal persons, especially in those over the age of 50, detracts greatly from the diagnostic value of abnormal records. The apparently normal subjects demonstrate a similar age trend, with older normal persons having a high incidence of abnormal BCGs.[3] No abnormal ballistocardiograms were found in normal controls under the age of 40, but thereafter a precipitous rise in incidence occurs, to 90 per cent in the eighth and later decades. These facts have led us to conclude that clinical significance might be attached to abnormal tracings in individuals under the age of 50 and to normal records in those over the age of 60. An obvious explanation for the high incidence of abnormal tracings in the older normal subjects is the presence of latent coronary atherosclerosis. Many ancillary sources of evidence suggest such an explanation, but until more definite proof of such causal relationship can be established in individual subjects, subclinical disease cannot be invoked as the solution to this problem. Many other factors, some noncardiac in nature, are potentially involved in BCG form abnormality.

Ultra-Low Frequency BCG in Coronary Disease: The studies thus far discussed have been performed on a high-frequency, Starr type ballistocardiograph. It has been shown that this, as well as the direct body devices, possess several sources of distortion, which are in large measure absent from the newer "ultra-low frequency" instruments.[4] A broad survey of the potential usefulness of these new methods has not yet been completed and it is not known whether a more decisive segregation of normals from patients is possible through the use of the ultra-low frequency methods. At present, adequate quantitative criteria for classification of the new patterns have not been completely determined.

In order to assess the usefulness of this instrument in coronary heart disease, in a preliminary and only qualitative manner, 100 random tracings were analyzed. These were from a larger series of as yet unclassified ultra-low frequency ballistocardiograms. Fifty records from clinically normal persons, ranging in age from 25 to 71 years, predominantly males, were compared with 50 records from patients with coronary artery disease, similarly distributed as to age and sex. The patterns were classified as normal, borderline, or abnormal, in order to facilitate over-all comparison with high frequency tracings from the same patients and classified in the same manner.[3] Table I summarizes this strictly preliminary qualitative survey. It is clear that abnormalities of form were found with greater frequency in patients with coronary heart disease when the newer ballistocardiographic method was employed. However, on the other hand, a higher incidence of borderline or abnormal tracings was also found in normal subjects. Obviously a detailed *quantitative* study may prove these *qualitative* estimates to be misleading but at this time it seems probable that qualitative interpretation of the ultra-low frequency tracing will not provide any greater separation of normal controls from patients than do the older methods.

"Stress" Tests

ECG Exercise Test: Because of the failure of the electrocardiograph and ballistocardiograph to fill the need for an objective means of detecting coronary atherosclerosis, several "stress" procedures have been employed in an effort to broaden the usefulness of the instruments. Doubtless the most widely used has been physical effort of varying type and degree. The most popular procedure has been the graded two-step test, using criteria established by Master.[5] This method has been investigated in our laboratory, monitored by ECG and BCG, with the former graded as described by Master and the latter as described elsewhere.[6]

The electrocardiographic exercise test, using the "single" and/or "double" method, was "positive" in 50 per cent of patients with clinical angina pectoris or old myocardial infarction. However, 114 normal control subjects, including many young females, showed a positive test in 23 per cent.[6] The high incidence of positive exercise tests in normal subjects has led us to suggest that the criteria established by Master for a positive response should be modified. Despite a still further decrease in diagnostic "yield," considerably greater specificity for the ECG exercise test is achieved if the degree of ST-T alteration required for a positive test is increased. We consider ST segment depression of 0.75–1.4 mm a "borderline" response and 1.5 mm or greater depression in any ECG lead (or T wave inversion in leads other than lead 3) a "positive" test. False positive tests, using these criteria, have not been found in our control subjects.

BCG Exercise Test: The ballistocardiogram recorded after exercise is difficult to evaluate because of artifactual influences. Despite this, efforts to determine the usefulness of the BCG exercise test as a diagnostic stress procedure were carried out.[6] Following the 2-step test 31 per cent of patients with coronary artery disease showed alterations from control form of a degree sufficient to be considered "positive." In the apparently normal subjects 8 per cent showed similar post-exercise ballistocardiographic deterioration. It thus seems clear, at least as far as experience in our laboratory indicates, that the stress of exercise, monitored by either the electrocardiograph or ballistocardiograph, fails to discriminate adequately the patient with coronary heart disease from healthy normals.

TABLE I

Qualitative Evaluation of Ultra-Low Frequency BCG Patterns Compared with Starr Bed (High Frequency) Tracing from the Same Individuals

Subjects	Ultra-low frequency			High frequency		
	Normal	Borderline	Abnormal	Normal	Borderline	Abnormal
Coronary disease: 38 males, 12 females	6 (12%)	13 (26%)	31 (62%)	14 (28%)	12 (24%)	24 (48%)
Normal controls: 39 males, 11 females	23 (46%)	16 (32%)	11 (22%)	37 (74%)	8 (16%)	5 (10%)

Other Stress Tests for Coronary Insufficiency: Other means of inducing cardiovascular stress have been studied by many investigators. Controlled *anoxemia*, monitored by the electrocardiograph and/or the ballistocardiograph, has been popular in some clinics. Our experience with this method is limited.[7] The intravenous administration of *ergonovine*, first suggested by Stein,[8] later more widely studied by Rinzler *et al.*,[9,10] shows promise of potential usefulness. Its effect in decreasing coronary blood flow in animals leads to electrocardiographic alteration following either its injection into the intact animal or upon the isolated, perfused heart. The effect of this agent on the ballistocardiogram in humans is under study at present, but sufficient data to warrant comment are not yet available. A representative

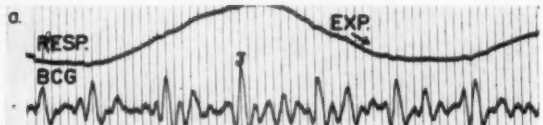

Fig. 1. The effects of the intravenous administration of 0.2 mg. ergonovine on the BCG of a 65-year-old male with angina pectoris: (a) represents the control pattern, which is within normal limits; (b) is the record 10 minutes after injection, with diastolic wave amplitude increasing; and (c) taken 20 minutes after injection shows variable distortion of systolic wave pattern and persistence of large diastolic waves.

response of a patient with coronary artery disease to ergonovine is shown in Figure 1. The frequency of such ballistocardiographic alteration in patients and in normal controls has not yet been determined. The parenteral administration of *pitressin*, the most potent known coronary vasoconstrictor, would seem to be of potential value as a stress procedure, but may be of danger out of proportion to its usefulness.

Spontaneous Coronary Insufficiency: Diagnostic alteration in the electrocardiogram or ballistocardiogram may occur during spontaneous coronary insufficiency, if one is fortunate enough to obtain such records under these circumstances. When gross ballistocardiographic form distortion, or electrocardiographic change in the ST segment or T wave is detected during an attack of angina pectoris, objectivity is clearly attained. Unfortunately, this occurs too rarely to satisfy the demands of routine laboratory study.

BCG Cigarette Test: In our experience to date, the most frequent objective abnormality found in patients with coronary artery disease is obtained with the ballistocardiographic cigarette test.[6,11] The ballistocardiograph is an instrument of great sensitivity and reflects

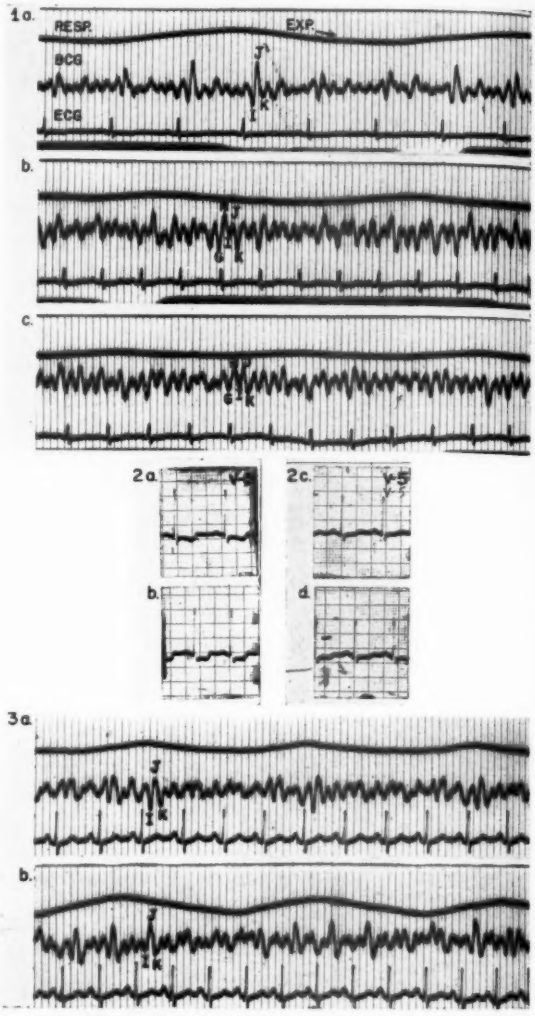

Fig. 2. The effects of cigarette smoking on the BCG and ECG. (1a) is the control BCG from a 46-year-old female with severe angina pectoris. This pattern is classified as "borderline." (1b and c) show the immediate and five-minute postsmoking records, demonstrating gross deterioration of pattern, large presystolic waves, accentuated G-H segment, and large diastolic waves. (3a and b) show immediate and five-minute postsmoking records, as obtained when the cigarette was preceded by sublingual nitroglycerin. Although some alteration of pattern occurs after smoking, the degree of distortion is clearly less when nitroglycerin is used. The electrocardiographic change is represented in (2a and b). (2a) is V_5 during control period, (2b) V_5 after smoking. ST segment depression is increased after smoking; in (2c and d), representing control and postsmoking observations, a definite decrease in the extent of ST displacement occurs when nitroglycerin precedes the cigarette.

changes in cardiovascular dynamics that result from routine smoking of a cigarette much more dramatically than does the electrocardiograph.

The latter occasionally shows dramatic alteration after smoking, as seen in Figure 2, but changes of this magnitude are seen in less than 1 per cent of patients with coronary artery disease. Minor T wave lowering is commonly observed after a cigarette, both in diseased patients and in normal control subjects, but the ballistocardiographic response to smoking is greater both in degree and in frequency. Approximately 50 per cent of patients with coronary artery disease show alteration of ballistocardiographic form (after smoking one cigarette) of sufficient degree to be considered "positive" reactors according to criteria previously described.[6,11] In contrast, only 7.5 per cent of normal subjects show this response, and these positive tests are largely found in males in older age groups, who presumably are candidates for latent atherosclerotic disease. A representative cigarette test is seen in Figure 2, which illustrates both electrocardiographic and ballistocardiographic reactions.

It is our feeling that a positive cigarette test should be looked upon with considerable suspicion and may be considered ancillary evidence of coronary heart disease. It should be emphasized that these observations were made on the high frequency instrument. Studies using ballistocardiographs of other types may not show specificity of the same degree. The ultra-low frequency instrument shows a lower incidence of positive tests in a preliminary survey in our laboratory, and the direct body method may possibly detect a higher number of positive reactors in apparently normal persons. Equally deserving of emphasis is the difficulty sometimes involved in interpreting and evaluating the cigarette response; in many instances the changes are concise and readily apparent, but in others considerable experience is necessary for adequate appraisal.

The Ballistocardiograph in Evaluation of Measures Thought To Be of Therapeutic Value

Perhaps the ballistocardiograph has its greatest current value as an auxiliary method in the appraisal of the effects of various therapeutic measures in patients with established coronary artery disease. Certain clinical observations in this laboratory would suggest that the usefulness of the method in this regard has been minimized in the past and warrants more consideration. The evaluation of patients with this disease is beset with difficulties, and emotional and related influences play a considerable role in determining symptomatic reaction. The effects of various therapeutic programs are best determined from mortality and longevity data; the objectivity of the ballistocardiogram has certain obvious advantages. In this regard the ballistocardiogram may not be as subject to extracardiac influences, since such factors as aortic elasticity, body damping, etc., presumably do not change. These and other physical features do play a role in determining the basal ballistocardiographic pattern, but probably are not as altered during therapeutic programs as basic cardiac dynamics. This aspect of ballistocardiographic reactivity applies perhaps even more strongly to its usefulness in the aforementioned stress procedures.

Estrogen Therapy: Recent observations in a small group of patients given estrogenic substances or synthetic compounds with estrogenic properties have been of interest in this regard.[12] The ballistocardiogram showed improvement in all of 11 patients given large dosages of conventional estrogens over an average test period of 14 months. In a larger number of subjects (27) with coronary heart disease given a new synthetic steroid possessing estrogenic activity on serum lipids (Manvene),[12] 50 per cent showed BCG improvement over an average drug treatment period of 7.3 months. Whether these changes are truly indicative of increased efficiency of myocardial function, or rather a reflection of alteration in physical properties of blood, change in vascular reactivity, or some noncardiovascular phenomenon, is not known. However, the association of ballistocardiographic and symptomatic improvement with increased exercise tolerance and favorable alteration of serum lipids would suggest that basic cardiovascular function is improved. Such improvement in the BCG in untreated patients with coronary heart disease occurred in only 6.5 per cent of our patients over a two-year-period of observation. Figure 3 shows repre-

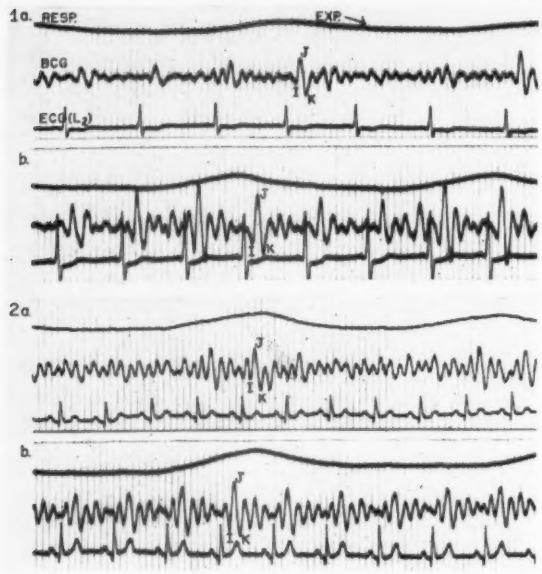

Fig. 3. BCG response to estrogen therapy in two patients with coronary disease. (1a) is the pretreatment tracing from a 46-year-old male who had previously sustained a myocardial infarction. The complexes are small in amplitude, and, except for those in mid-inspiration, are abnormal in form. (1b) is the same patient after 9 months' treatment with 10 mg of diethylstilbestrol daily. (2a) is the control pattern from a 59-year-old female with severe angina pectoris. (2b) shows the BCG after 11 months of treatment with Manvene, a new synthetic estrogen, 10 mg daily. Both posttreatment tracings show improvement in form, actually to essentially normal patterns.

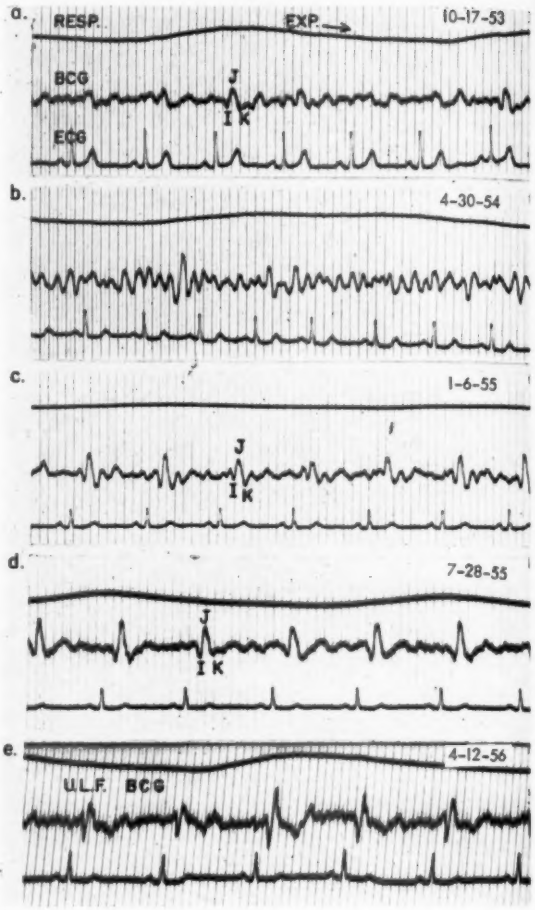

Fig. 4. The effects of radioactive thyroid ablation in a 54-year-old female with severe angina pectoris: (a) is a control tracing, which is abnormal in form, and of low amplitude; (b) shows a pretreatment tracing recorded during an episode of spontaneous angina with BCG deterioration; (c) and (d) were recorded after hypometabolism had been induced and the BCG improvement, actually to almost normal form, correlated well with the striking clinical improvement which resulted from this form of therapy; (e) is a normal ultra-low frequency tracing, obtained even later in the posttreatment period.

sentative tracings in two patients under estrogen therapy.

Radioactive Iodine Therapy: Although our experience with hypometabolic treatment of coronary heart disease is less extensive, several patients have been followed in whom the ballistocardiogram closely reflected the degree of clinical improvement following radioactive iodine therapy. Figure 4 is representative of this type of therapeutic response. This patient, a 54-year-old female, had severe angina pectoris, consuming more than 50 nitroglycerin tablets daily, prior to radioiodine thyroid therapy. After therapy she was followed for many months during which *no* nitroglycerin was necessary. The ballistocardiographic pattern can be closely correlated with the subjective improvement.

Dietary Fat Restriction: Perhaps more difficult to evaluate is the patient treated with dietary fat restriction. Degree of adherence to such a program is often not complete, but in a recent survey of a large number of patients to whom such a diet had been given, 36 patients faithfully followed the prescribed diet for six months to three years (average two years). These diets included 20–40 g total fat daily. In this group, 30 per cent have shown definite improvement in ballistocardiographic pattern; this was significantly higher than in a large control group on an unrestricted diet (6.5 per cent). It seems probable that this is another sphere in which the BCG may be of value in assessing the effect of therapy upon myocardial function.

Surgical Revascularization Procedures: The evaluation of patients treated surgically with one of the many revascularization procedures is notably difficult. An effort to utilize the ballistocardiograph in such an appraisal is currently in progress. Sixteen patients have been studied in our laboratory before and at various intervals after a procedure performed by Dr. David Sabiston. This operation is a modification of the technic reported by Harken.[18] In the immediate postoperative period the ballistocardiogram usually shows, as might be anticipated, deterioration of form. Late postoperative studies are limited at this time, but the changes in some patients have been gratifying. Representative tracings are shown in Figure 5; in this patient the ballistocardiographic improvement was accompanied by modest but definite clinical improvement. No conclusions can be drawn from the short periods of observation and small number of patients but it is hoped that the BCG will assist in the evaluation of this and other surgical methods of treatment in the future.

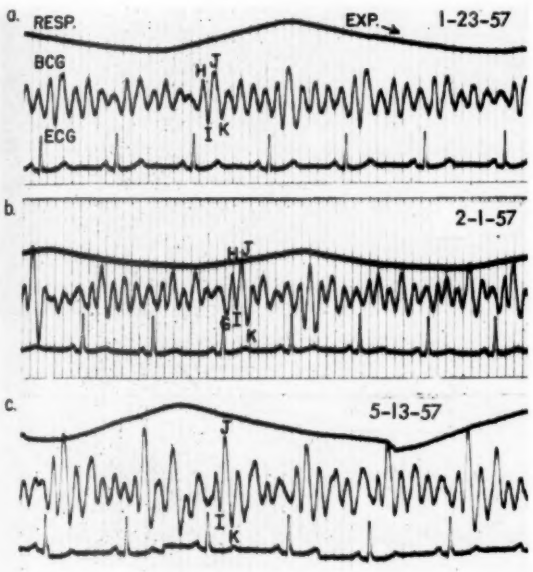

Fig. 5. The effects of revascularization surgery in a 52-year-old male with angina pectoris: (a) is the preoperative BCG, which is slightly abnormal, showing prominent H waves; (b) is a record one week after de-epicardialization and talc poudrage; BCG form is more abnormal at this stage; (c) is a tracing four months after operation and record has become normal.

Conclusions

The ability of the clinician to demonstrate objectively the presence of coronary disease with currently available technics is severely limited. The shortcomings of the resting electrocardiogram and ballistocardiogram have been demonstrated. The addition of various types of cardiovascular "stress" have been considered and the failure of most of the standard forms of stress, especially exercise, to differentiate adequately normal subjects from patients with coronary insufficiency has been shown. The usefulness of the ballistocardiographic cigarette test has been emphasized. Other forms of stress, especially the ergonovine test, have been suggested as having potential usefulness.

The ballistocardiograph as a monitor of various therapeutic measures has been described. Correlation with clinical improvement has been shown under several treatment conditions, including estrogens, diet, hypometabolic, and surgical programs. The potential value of the BCG as a therapeutic guide is discussed.

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The Ballistocardiogram After a Heavy Meal

Diagnostic Value in Patients with Suspected Coronary Artery Disease

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ANGINA PECTORIS due to coronary artery disease is one of the most difficult of all heart diagnoses to make. Despite a suggestive or even a typical history, graphic objective proof is desirable. The electrocardiogram is usually normal in 50 per cent of cases of coronary artery disease. The ECG exercise tolerance test is positive in 10 to 15 per cent of the cases with normal resting electrocardiograms. Because of these facts, it was decided to turn to ballistocardiography as a possible means of making a more accurate clinical diagnosis.

The results of previous ballistocardiographic studies were: (1) Normal people under 45 usually had normal ballistocardiograms.[1] (2) As age increased, the tendency to abnormal ballistocardiograms in apparently normal people increased. (3) Only 15 per cent of apparently normal people over 70 had normal ballistocardiograms. This may mean that those people over 45 who have abnormal ballistocardiograms and who are apparently normal, may not be.[2] These people may have asymptomatic coronary artery disease.

The recording of the ballistocardiogram after a heavy meal has been considered a more accurate test in patients suspected of having coronary disease.[3] This paper presents a preliminary report of our results with this ballistocardiographic method as a test of coronary insufficiency.

CLINICAL OBSERVATIONS

In order to evaluate the test properly, 40 normal people from 30 to 50 years of age were studied as controls. Twenty individuals with possible coronary disease were also studied. These patients had symptoms suggestive of coronary artery disease but the electrocardiogram at rest and after exercise and the resting ballistocardiogram were normal.

The test meal consisted of one pound of steak, one serving of potatoes, one cup of coffee, and a piece of pie. The BCG was recorded before the meal and thirty minutes after completion of the meal.

The only change in the 40 normal individuals was an increase in the amplitude of the H, I, J, and K waves (Fig. 1). In the series of 20 cases

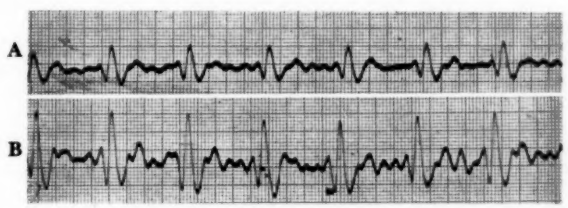

Fig. 1. BCG of normal patient before (A) and 30 minutes after (B) heavy test meal. Note the increased amplitude of the H, I, J, and K waves after meal (B). This is a normal test.

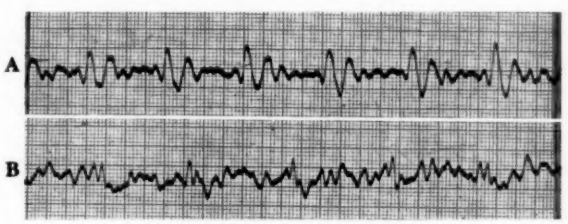

Fig. 2. BCG before (A) and after (B) heavy test meal in patient with suspected coronary disease. Note the normal BCG in (A) and the deterioration of the record in (B). This patient had a normal ECG at the time of this test but it became abnormal three years later.

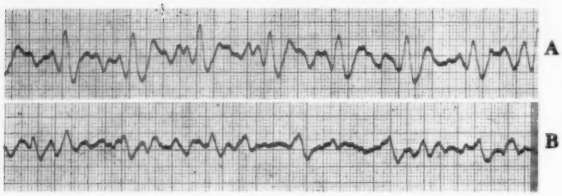

Fig. 3. BCG before (A) and after (B) heavy test meal in patient with suspected coronary disease. Note the marked deterioration of all components of BCG in (B). Four years after this test the ECG remained normal but the Master exercise test became positive.

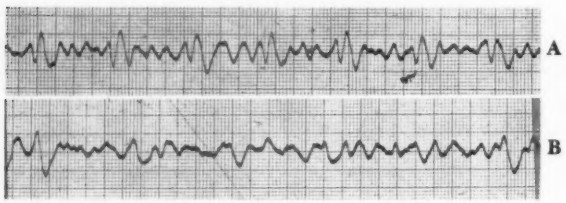

Fig. 4. BCG before (A) and after (B) heavy test meal in patients with suspected coronary disease. This is a positive test. Note the marked deterioration of all BCG components in (B). Three years after this test the ECGs at rest and after exercise are still normal. However, the patient is having increasing symptoms of coronary insufficiency.

with suspected coronary disease, 12 BCG's deteriorated after a heavy meal (Figs. 2 to 4) and 8 showed no changes.

Follow-up Observations: The 12 patients who had abnormal ballistocardiograms after the heavy-meal test were studied and followed for six years. Five of these later developed an abnormal resting electrocardiogram (Fig. 2). Five others have a normal electrocardiogram but a positive ECG exercise test (Fig. 3), and the remaining two have increased symptoms of coronary artery disease (Fig. 4) but no definite graphic proof of this condition is evident. Of the 12 cases, three have developed myocardial infarcts. Of the eight individuals who had normal ballistocardiograms after a heavy meal none has developed any trouble whatsoever to date.

Conclusion

The results so far suggest that the heavy meal ballistocardiograph test may be another means of proving the presence of coronary artery disease. A larger series of cases with follow-up study is indicated, and we are proceeding with these studies.

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Report on Therapy

Some Observations on the Pharmacology of Hydrochlorothiazide*

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THE DISCOVERY of chlorothiazide has been a major development in diuretic therapy. It is as effective when given orally as when given by the parenteral route. The primary effect appears to be inhibition of renal tubular reabsorption of sodium and chloride resulting in a secondary increase in water excretion. There appears to be some carbonic anhydrase inhibitory effect on the renal tubules, particularly at larger doses.[1]

In an attempt to improve the potency and decrease the incidence of certain side effects, a number of benzothiadiazine derivatives were synthesized by Novello and Sprague. The report includes our observations on the clinical pharmacology of hydrochlorothiazide (Hydrodiuril),† a compound which differs from chlorothiazide only in that the heterocyclic ring has been saturated by the addition of two hydrogen atoms (Fig. 1).

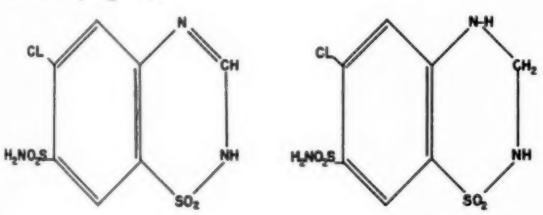

Fig. 1. Chemical structure of chlorothiazide and hydrochlorothiazide.

METHODS

1. Hydrochlorothiazide Excretion Studies: The excretion rate of hydrochlorothiazide was studied in 5 normal subjects (group 1). These were hospitalized patients who remained supine throughout the study. Immediately upon awakening in the morning they were each given 250 ml of water which was repeated hourly throughout the study. One hour after drinking the first water the experiment was begun. Two one-hour urine control collection periods were first obtained. Then 1,500 mg of hydrochlorothiazide were given orally. Subsequently urine was collected hourly for four to six hours. The urine was then analyzed for sodium, potassium, and chloride content. The amount of hydrochlorothiazide excreted each hour was determined.

2. *Dosage Response Curve:* A group of 18 patients (group 2) were given different doses of hydrochlorothiazide. The first patients received 400 mg daily (200 mg twice a day). Subsequently, the dose was either decreased by 50 per cent or doubled; thus log doses were available for determining the dose response curve of the drug.

The bioassay studies were conducted using normal subjects or patients with mild heart failure who had previously demonstrated evidence of edema but who at the time of the study were edema-free. Hydrochlorothiazide was given to these patients for three successive days. They drank 2,500 ml of distilled water per 24 hours and consumed a diet containing 50 meq of sodium per 24 hours. Twenty-four-hour urine specimens were collected and analyzed for sodium, potassium, chloride, and volume. The patients were weighed each morning before breakfast and after voiding. After suitable control periods, the patient's urinary excretion rate of sodium was approximately 90 to 95 per cent of the dietary sodium intake. The patient's excretion rate of sodium continued at this constant level for at least two days before the drug was given.

The patient was then given a single dose of the experimental drug after breakfast for three consecutive days, and the body weight and excretion rates of water and electrolytes were determined. After the drug was stopped, the patient's excretion rate of sodium usually de-

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† Supplied by Merck Sharp & Dohme, Inc., as Hydrodiuril®.

creased for one to three days, during which time the body stores of sodium were replenished and the patient once more began to excrete at a fairly constant rate, which was very close to his dietary sodium intake.

The minimum dose of hydrochlorothiazide administered was 25 mg, since this dose seemed to produce a minimal response. The maximum dose used was 1,000 mg given twice a day. It was possible to increase the dose in an incremental fashion in each patient until further increases in dosages did not produce a significantly greater increase in the excretion of sodium. This same procedure has been used to establish the maximum effect of chlorothiazide and of carbonic anhydrase inhibitors.[2] After the dose was established which produced maximum natriuresis in the majority of the patients, a dose of at least two times this dose was given. Methods and technics have been described previously.[2]

3. *Renal Hemodynamic Studies:* In order to evaluate the renal response to hydrochlorothiazide, observations were made on the glomerular filtration rate and the renal plasma flow (group 3). Inulin was used to determine glomerular filtration rate and paraaminohippurate to determine renal plasma flow. Methods and technic have been described previously.[3,4] After three successive control periods were obtained, 200 mg of hydrochlorothiazide were given intravenously. Successive 30-minute collection periods were then made for five hours after drug administration.

4. *Observations in Outpatients:* A group of 20 patients (group 4) with heart failure was observed in the outpatient clinic. All diuretics were withdrawn for a period of five days. Otherwise there were no alterations in their therapeutic programs. After five days when the patients returned to the clinic they were weighed and a brief history and physical examination were recorded. Ten of the patients (subgroup A) then received 50 mg of hydrochlorothiazide once daily and 10 (subgroup B) received 100 mg every 12 hours for the next 10 days. The patients were seen twice during this period of time and their weights were recorded, along with the observations made by history and physical examination.

Another group of 19 patients (group 5) were studied under similar circumstances. Following suitable control observations during which the patients did not receive diuretics for a period of 10 days, 15 of these patients were first given 500 mg of chlorothiazide twice daily continuously for a period of three days. All diuretics were then stopped again for 10 days. This served as the second control period. The patients were now given 250 mg of hydrochlorothiazide every 12 hours for three days, during which time observations were made on weight response and symptoms.

Results

1. *Hydrochlorothiazide Excretion:* The observations made on the excretion rate of hydrochlorothiazide are summarized in Figure 2. Hydrochlorothiazide appeared in the urine within one hour following oral administration. It reached maximum excretion within three hours, but less than 25 per cent of the entire amount of the drug ingested was excreted within five hours. The plasma level reached maximum concentration within the first two hours and rarely exceeded 6 μg per ml of plasma. This concentration of drug persisted throughout the period of observations, suggesting continuous absorption. The diuretic effect of the drug paralleled the excretion of this compound in the urine.

Interestingly enough, the primary effect seemed to be on chloride excretion (Fig. 3). In contrast to chlorothiazide, there was nearly

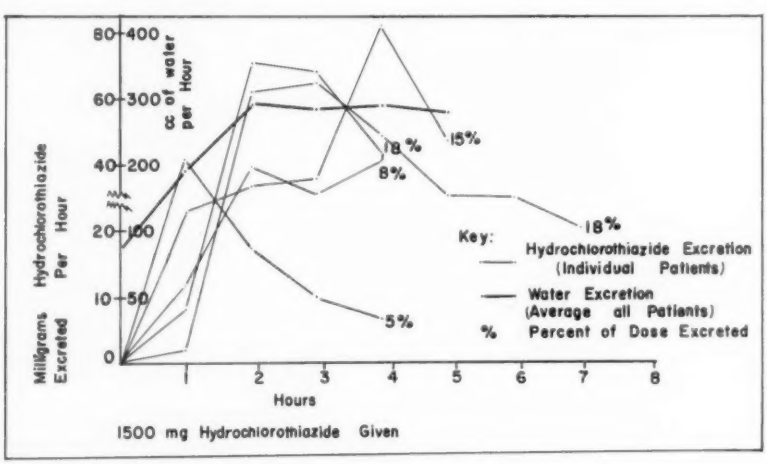

Fig. 2. Excretion rate (hourly) of hydrochlorothiazide after large single oral dose (1,500 mg) in five patients.

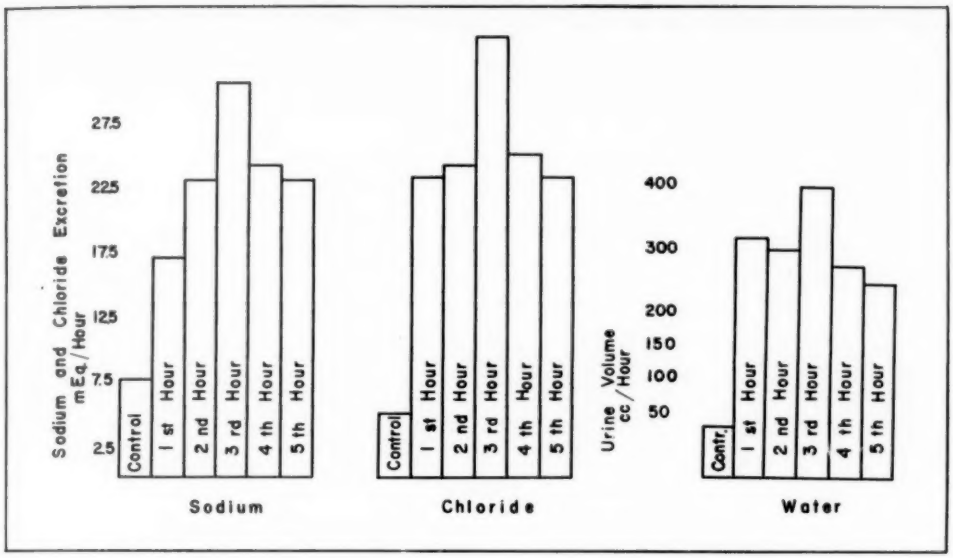

Fig. 3. Response to a single oral dose of hydrochlorothiazide (1,500 mg).

always a greater increase in chloride excretion than in sodium excretion. Bicarbonate excretion was not affected in a predictable way, although there was sometimes a slight increase. Potassium excretion increased but not to the same degree that sodium did.

2. *Dosage Response Curve:* The observations on sodium excretion indicate a minimal response to a single daily dose of 25 mg of hydrochlorothiazide (Fig. 4). As the dose is increased there is an increasingly greater excretion of sodium until a dose of 400 mg is reached, at which point there is no further increase in natriuresis. In fact, when the dose exceeds 800 mg there appears to be a sharp decrease in the natriuretic response to the drug. Although these are preliminary observations, the response observed appears to be very real and is difficult to explain unless it is evidence of renal tubular toxicity. The dose of hydrochlorothiazide

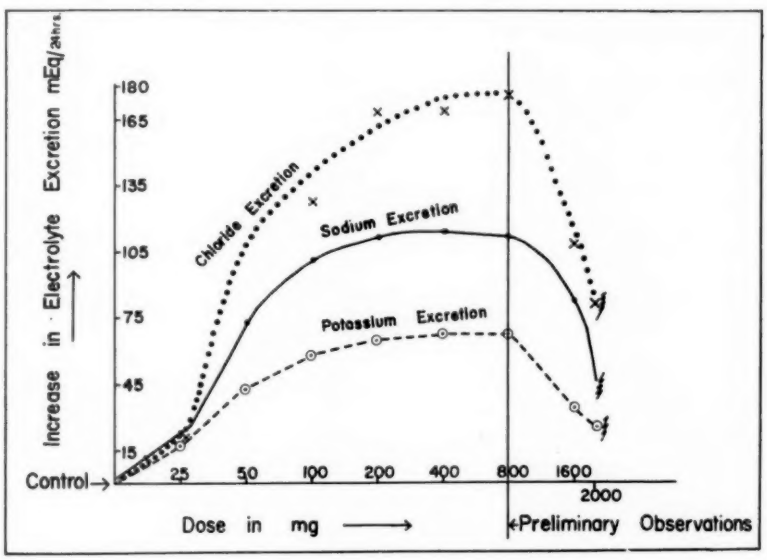

Fig. 4. Dose response curve—hydrochlorothiazide.

should not exceed 100 mg given twice a day.

As in the acute studies, the primary effect in these 24-hour excretion studies also seemed to indicate a greater increase in chloride excretion than in sodium, associated with a very definite increase in potassium excretion.

3. *Renal Hemodynamic Studies:* Immediately following administration of the drug intravenously, there was a temporary reduction in the glomerular filtration rate. This returned to control values within one hour. Despite the temporary decrease in the glomerular filtration rate, there was an increase in salt and water excretion. Paraaminohippurate excretion increased slightly (Fig. 5). It can be concluded

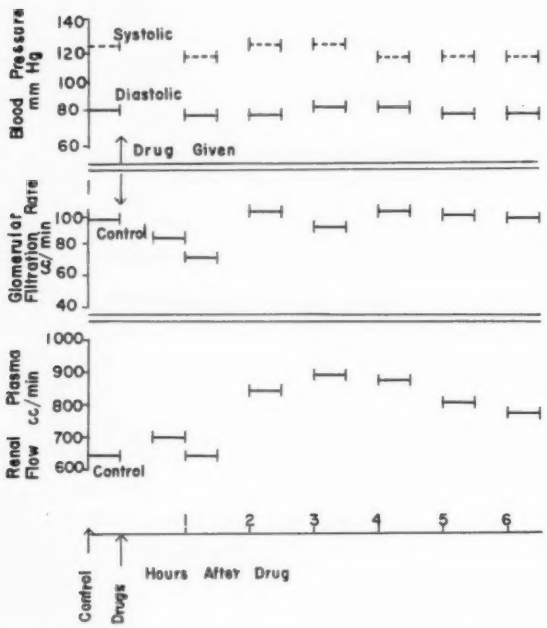

Fig. 5. Renal hemodynamic and blood pressure response to 200 mg hydrochlorothiazide intravenously.

from these observations that the diuretic and natriuretic effect of the drug is a tubular response and is not due to an increase in the glomerular filtration rate.

4. *Outpatient Clinic:* The patients in heart failure treated in the outpatient clinic showed an inadequate response in weight loss when given 50 mg of hydrochlorothiazide daily. The average weight loss was 0.4 pounds ($p>0.50$). In the patients given 100 mg twice a day, there was an average weight loss of 3.5 pounds ($p<0.01$).

When the response of the patients who received 500 mg of chlorothiazide (Diuril) twice a day is compared with those who received 250 mg of hydrochlorothiazide twice a day, the response was nearly the same, being 2.4 pounds ($p<0.05$) and 2.7 pounds ($p<0.05$), respectively. Symptoms were equally well controlled on both drugs.

Comments

It is of some interest to compare the dose response curves of chlorothiazide, flumethiazide* and hydrochlorothiazide. The maximum effective dose of both chlorothiazide and flumethiazide appears to be 1,000 mg twice a day, whereas the maximum effective dose of hydrochlorothiazide appears to be 100 mg given twice a day. When the dose of hydrochlorothiazide is increased to 800–1,000 mg twice daily, the natriuretic effect is much less than the response to the 200 mg dose. The minimal dose which appears to produce definite natriuresis is 20 to 25 mg of hydrochlorothiazide, 125 to 250 mg of chlorothiazide, and 300 to 400 mg of flumethiazide. By contrast to hydrochlorothiazide, the primary effect of flumethiazide is on natriuresis and not chloruresis. The latter compound also has less effect on potassium excretion than do chlorothiazide and hydrochlorothiazide.

Conclusions

(1) Hydrochlorothiazide is an effective diuretic, natriuretic, and chloruretic agent. The chloruretic response appears to be greater than the natriuretic response.

(2) A dose of 100 to 200 mg of hydrochlorothiazide given twice a day seems to be equally as potent in its natriuretic effect as 1,000 mg of chlorothiazide given twice a day.

(3) When the dose of hydrochlorothiazide exceeds 800 mg the natriuretic, chloruretic, diuretic, and even the kaluretic response decreases. This may indicate renal tubular toxicity in larger doses.

(4) Because of the decreasing effectiveness with larger doses and the potential renal alkalosis, this drug should be given extensive and prolonged clinical trial before it is released for general use. The daily dose of the drug should not exceed 100 mg given twice a day.

* Flumethiazide is the trifluoromethyl thiazide derivative of chlorothiazide furnished by E. R. Squibb and Company.

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Case Reports

Urticaria after Administration of Warfarin Sodium*

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WARFARIN SODIUM,† which is 3-(α-acetonylbenzyl)-4-hydroxycoumarin sodium, is a synthetic anticoagulant that was isolated in the laboratories of Dr. Karl P. Link.[1] It has become widely used recently because of its rapid onset of action and relatively stable maintenance dose.[2–5] Further, its solubility permits parenteral administration.[4–6] Toxic manifestations other than those due to its anticoagulant properties have not been described in its administration to nearly 800 patients.[2–5,7–16] In addition, approximately 200 patients have received warfarin at the Mayo Clinic since the report of Wolff and associates.[16] This is the first report of an urticarial reaction to develop after administration of this agent.

REPORT OF CASE

A 50-year-old white man came to the Mayo Clinic on August 28, 1957, because of cyanosis and mild discomfort in his right great toe. He had suffered from progressive, bilateral, intermittent claudication of the buttocks, thighs, and calves for 10 years. In February, 1956, the left great toe suddenly had become cyanotic and remained so until bilateral lumbar sympathectomy was performed two months later. This procedure caused subjective increase in warmth of both legs and feet, with complete healing of a superficial cutaneous infarct in the left great toe. The intermittent claudication continued unabated. On August 19, 1957, the right great toe suddenly had become cyanotic and moderately painful. This did not improve, and he came to the clinic nine days later.

On examination, the pertinent findings included absent pulsations in the major arteries below the abdominal aorta, minimal postural changes in color, and a delay of 30 sec in venous filling in both feet. The right great toe and, to a lesser extent, the right second toe exhibited mottled cyanosis. Tenderness was absent. Examination of the optic fundi revealed full retinal veins, with one small superficial zone of hemorrhage in the right eye; the diagnosis of polycythemia was suggested by the ophthalmologist.

Values for blood urea and sugar, plasma cholesterol, fatty acids and phospholipids, serum uric acid, and blood coagulation time and prothrombin time were within normal limits. Special tests for coagulation accelerators gave normal results. Urinalysis revealed grade 2‡ pyuria, but a culture gave no growth. The value for hemoglobin was 17.8 g/100 ml of blood; the volume of packed cells (hematocrit) was 60 per cent; leukocytes numbered 9,300 per cubic millimeter, with a normal differential count. A smear of peripheral blood was not remarkable. The platelet count was 119,000. The blood volume was determined utilizing Congo red; the plasma volume was 26 ml/kg/body weight, and the erythrocyte volume was 38 ml. Electrocardiograms, as well as roentgenograms of the thorax, were not remarkable. Roentgenograms of the abdomen revealed calcification of the abdominal aorta and hypertrophic changes and osteoporosis of the lumbar portion of the spinal column.

Clinical Course: The patient was considered to have aortoiliac occlusion and relative polycythemia, with recent digital arterial occlusion in the right great toe. He was treated with whisky (as a vasodilator) and was placed on an oscillating bed for eight hours each day. A therapeutic heating box was placed over his feet. A combination of equal parts of secobarbital sodium and amobarbital sodium (Tuinal) was administered at bedtime throughout his stay in the hospital. Venesection, with removal of 500 ml of blood, was done on two occasions, reducing the hematocrit reading to 47 per cent. Surgical repair of the aortoiliac occlusion was consid-

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† Supplied as Coumadin sodium, Endo Laboratories.

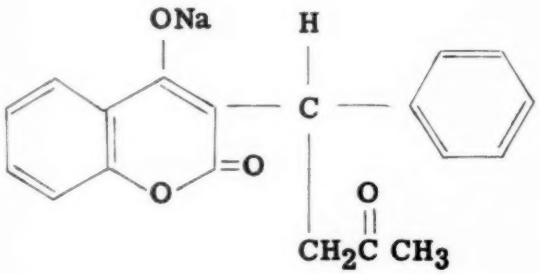
‡ Grading is on a basis of 0 to 4.

ered but was deferred because the claudication was not incapacitating and it was problematic that the high occlusion was contributing significantly to the acute ischemia of the right great toe.

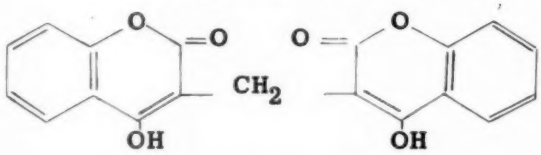
It was decided that long-term therapy with anticoagulants might prevent further occlusion of the small vessels; accordingly, he was given 50 mg of warfarin sodium by mouth on September 4. Generalized urticaria developed 40 min later. He was relieved by the oral administration of 50 mg of diphenhydramine (Benadryl), and the rash completely subsided in two days. The Quick prothrombin time increased to 36 sec by September 6 and was again 20 sec by September 8 (normal is 19 sec). On this day he was given 25 mg of bishydroxycoumarin (dicumarol) by mouth without untoward effect. He received dicumarol subsequently in doses sufficient to keep the prothrombin time between 35 and 45 sec. On September 15, test doses of warfarin sodium in dilutions of 1:1000 and 1:100 in an isotonic solution of sodium chloride were injected intracutaneously into the patient and a control subject, with no reactions. On September 17, only a healing superficial cutaneous infarct was present on the right great toe, and the patient was dismissed to continue anticoagulant therapy for an indefinite period and to have the hematocrit reading maintained at about 50 per cent by repeated venesection.

Comment

The appearance of an urticarial reaction so soon after the oral administration of warfarin sodium suggested a causal relationship. No other medications were being administered except whisky and Tuinal, and the patient continued to take these without further difficulty. The skin tests were not confirmatory, but this is often the case with oral antigens. It was not considered judicious to repeat the oral dose of warfarin sodium.



3-(α-acetonylbenzyl) -4-hydroxycoumarin sodium (warfarin sodium)



3,3′ -methylenebis (4-hydroxycoumarin) (dicumarol)

Fig. 1. Structural formulae of warfarin sodium and bishydroxycoumarin (dicumarol).

The subsequent administration of dicumarol without incident is of some interest, for it demonstrates an absence of cross sensitivity, although these agents are related chemically (see Fig. 1). The incidence of dermatitis associated with the use of dicumarol has been reported as 0.2 per cent,[17] although no comment on this complication was made in two large studies involving 5,611 patients.[18,19]

The relationship of the relative polycythemia to the acute digital arterial occlusion is not clear. Although the incidence of acute arterial occlusion is increased in patients who have polycythemia vera,[17,20] this has not been noted in relative polycythemia.[21]

Summary and Conclusions

Acute transient urticaria appeared in a 50-year-old man 40 minutes after oral administration of 50 mg of warfarin sodium. Subsequently, dicumarol was given without incident. Urticaria following administration of warfarin sodium must be rare, as it has not been reported previously. This does not detract from the clinical usefulness of this anticoagulant drug.

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Unusual Sensitivity to Digitalis

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DESPITE the fact that digitalis intoxication is well recognized clinically and electrocardiographically, it seems worthwhile to present this case report because it represents an unusual sensitivity to the ordinary maintenance dosage of one of the cardiac glycosides. Digoxin (Lanoxin) is a glycoside of digitalis lanata, whose rate of excretion is intermediate between that of cedilanid and digitoxin. In all other respects, it exerts the same cardiac action as do any of the other digitalis preparations.

In the following case report of an elderly white male, unusual electrocardiographic responses were obtained following the oral administration of 0.25 mg digoxin daily. Since there were no subjective complaints, the amount of daily digoxin was varied from time to time over an observation period of 20 months.

CASE HISTORY

H. B., an 80-year-old white male, was first seen in the office on June 17, 1955 complaining of nocturnal cough. He had recently been treated at home for bronchopneumonia and mild congestive failure. Past history was noncontributory. Physical examination revealed a slightly dyspneic, elderly white male, not acutely ill. Coarse moist rales were heard at the left lung base, and rhonchi were present at the right lung base. The blood pressure was 110/50. The heart sounds were of poor quality, and the rhythm was regular with a rate of 70 per minute. No murmurs were heard. The liver was not felt and there was no ankle edema.

Fluoroscopic examination of the chest revealed a dilated aorta and a rounded left ventricular border. The 12 lead electrocardiogram was entirely within normal limits. Urinalysis showed no abnormalities.

The patient was placed on 0.25 mg digoxin daily. Within a short time the nocturnal cough completely disappeared. The digoxin was continued. Three and a half months later, he was noted to have a pulse rate of 40/min with regular rhythm. He had no complaints and the physical examination was otherwise unchanged.

The digoxin was reduced to 0.25 mg on alternate days. One month later the cardiac rate was 92/min and regular. Thereafter the digoxin dosage was varied according to Table I. Finally on February 4, 1957 the glycoside was discontinued. Throughout the entire period of observation there were no subjective complaints. On March 4, 1957, without any medication, the P-R interval was 0.32 sec. One month later, the P-R interval fell to 0.22 sec. At this point, 0.05 mg of Acylanid was administered daily. However, after one month of Acylanid, an electrocardiogram revealed Wenckebach phenomenon. The pulse rate was 60/min and irregular. All cardiac drugs were discontinued.

DISCUSSION

It is clear from an examination of the records in this case that we are dealing with unusual sensitivity to both digoxin and Acylanid. Apparently the sequence of events resulting in the Wenckebach phenomenon in this patient was as follows: After one month of daily administration of 0.25 mg of digoxin, first stage heart block ensued; after the second month, the P-R interval became so prolonged that second stage

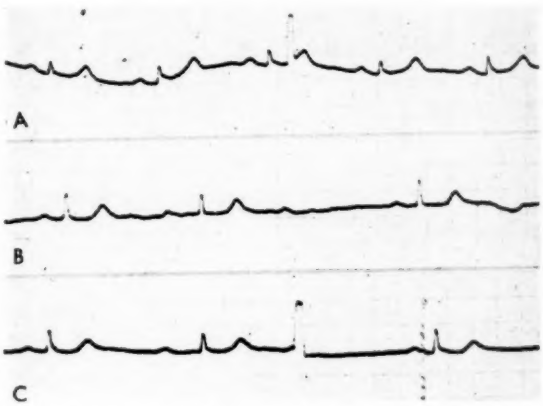

Fig. 1 (A). Control tracing, lead 2, before digoxin administration; P-R interval measures 0.20 sec. (B) After digoxin 0.25 mg daily for two months; partial heart block with Wenckebach phenomenon. (C) Digoxin dosage halved for one month and then 0.25 mg daily resumed for two months; recurrence of partial heart block.

TABLE I

Pulse Rate and Electrocardiographic Changes with Varying Digoxin Administration

Duration of digoxin administration	Pulse rate at end of interval	Electrocardiogram at end of interval
Daily for 3½ months	40, regular	None taken
Alternate days for 1 month	72, regular	None taken
Daily for 2 months	42, irregular	Wenckebach phenomenon (Fig. 1B)
Alternate days for 1 month	64, regular	None taken
Daily for 2 months	44, irregular	Wenckebach phenomenon (Fig. 1C)
Alternate days for 2 months	66, regular	P-R = 0.32 sec (Fig. 2A)
Daily for 1 month	56, irregular	Wenckebach phenomenon
Alternate days for 3 months	60, regular	P-R = 0.32 sec
None for 2 months	72, regular	P-R = 0.24 sec (1 month, Fig. 2B)
		P-R = 0.20 sec (2 months, Fig. 2C)
Daily for 2 months	72, regular	P-R = 0.22 sec (1 month)
	42, irregular	Wenckebach phenomenon (2 months, Fig. 3A)
None for 2 months	60, regular	P-R = 0.32 sec (1 month, Fig. 3B)
	72, regular	P-R = 0.22 sec (2 months, Fig. 3C)
Acylanid 0.05 mg daily, 1 month	42, irregular	Wenckebach phenomenon

block with Wenckebach phenomenon occurred. When the digoxin was stopped, the prolonged P-R interval persisted for a month, and finally returned to normal toward the end of the second month. These changes are demonstrated serially in Figures 1 and 2.

In order to determine whether sensitivity occurred to digoxin exclusively, a small dose of 0.05 mg Acylanid daily was administered for one month. This procedure was started two months after cessation of digoxin, at which time the P-R interval had returned to normal. Figure 3 demonstrates the Wenckebach phenomenon which was observed after one month on 0.05 mg of Acylanid daily. It is thus apparent that the sensitivity response in this patient may be obtained from several glycosides of digitalis. When one considers the small daily dosages involved, the striking effect on A-V conduction is all the more remarkable, since no initial digitalizing doses were used.

It is generally agreed that such unusual sensi-

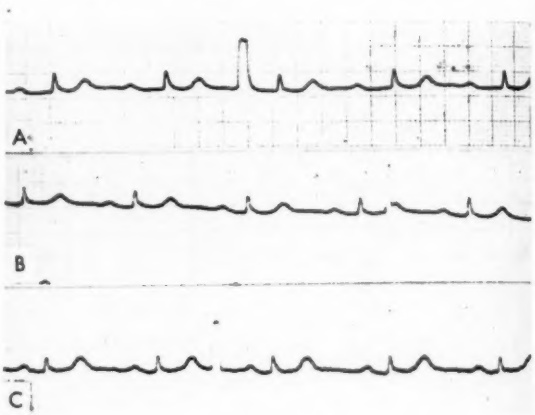

Fig. 2 (A). Digoxin dosage reduced to 0.25 mg on alternate days for two months; first stage block with prolonged P-R interval (0.32 sec). (B) Digoxin discontinued for one month; P-R measures 0.24 sec. (C) Digoxin discontinued for two months; P-R measures 0.20 sec.

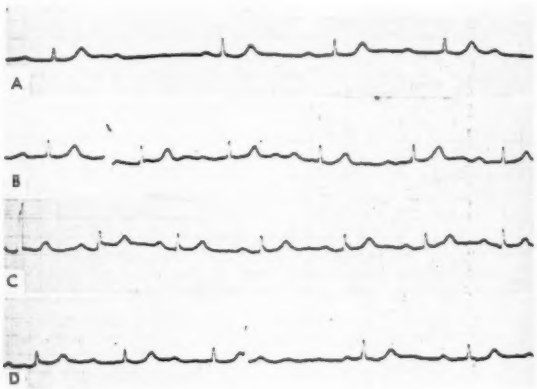

Fig. 3 (A). Third trial of digoxin 0.25 mg daily for two months; recurrence of partial A-V block with Wenckebach phenomenon. (B) One month after discontinuing digoxin; P-R interval measures 0.32 sec. (C) Two months after stopping digoxin; P-R 0.22 sec. (D) After one month on Acylanid 0.05 mg daily; reappearance of second stage partial heart block.

tivity to digitalis occurs more frequently in the older age groups.[1] Segal[2] reported a case of an 81-year-old woman who developed short runs of ventricular tachycardia following the administration of $1^1/_2$ gr of digitalis leaf daily for six months. The rhythm became regular six days after digitalis was stopped. In his case, no clinical symptoms of digitalis intoxication were observed. The frequent absence of symptoms in digitalis intoxication is well known. In 21 per cent of a series of 100 cases of digitalis intoxication, only electrocardiographic signs in the absence of symptoms were observed.[1] In this particular series there was no case reported among patients treated with cedilanid or digoxin. This observation concerning digoxin may be more apparent than real because of the few cases in this series treated with this glycoside.

Just exactly why elderly patients should be more sensitive to the effects of digitalis preparations than younger age groups is not clear. Raisbeck[3] and Master[4] feel that elderly cardiacs require smaller digitalis dosages than younger age groups. It is possible that some of the sensitivity in the aged may be mediated through the carotid sinus, since it is well known that digitalis increases the sensitivity of the carotid sinus. Furthermore the carotid sinus mechanism is more sensitive in the older age groups.

Summary

(1) A case of digitalis intoxication in an elderly patient is reported in whom electrocardiographic signs of impaired A-V conduction without symptoms were the sole manifestations.

(2) This patient presented abnormal electrocardiographic findings on small oral maintenance dosage of digoxin, without prior digitalization.

(3) Attention is called to the fact that in the elderly, digitalis intoxication due to small doses of any digitalis glycoside may be manifested by electrocardiographic signs alone (prolonged P-R interval or partial heart block). The recognition of this phenomenon is of great practical importance in the management of the patient.

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Electro-Vectorcardiography

A Simple Method of Studying Vectorcardiography, Using the Conventional Electrocardiogram*

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RECENT work has indicated that the vectorcardiogram is able to show signs of abnormalities which are not obvious in the conventional electrocardiogram.[1,2] However, since there is a close, actually an exact, mathematical relation between the vectorcardiogram and the electrocardiogram, it should be possible to find all abnormalities in the electrocardiogram which are recorded by the vectorcardiogram. One method of doing this is to derive the vectorcardiogram from the electrocardiogram.[1] For this reason, we have called this method *electro-vectorcardiography*.

From a clinical point of view, the most important use of vectorcardiography is in the diagnosis of right ventricular hypertrophy. One reason for this is that the presence or absence of right ventricular hypertrophy may be a decisive factor in determining whether a patient with mitral stenosis is a candidate for mitral valve surgery, or in determining the exact site of a congenital cardiac lesion.

In this paper, we shall first briefly describe the principles of vectorcardiography, and then shall describe a simple method of deriving the vectorcardiogram from the electrocardiogram. Finally, we shall show the application of this method to the diagnosis of right ventricular hypertrophy.

THE VECTORCARDIOGRAM

Methods of measuring the electrical axis of the heart from any two standard leads, using the Einthoven triangle, are well known.[3] This can also be done from leads 1 and aVF, using a rectangular coordinate system.[1] When the electrical axis is ordinarily measured, it is done for only one instant in the cardiac cycle. However, if the electrical axis were calculated and plotted

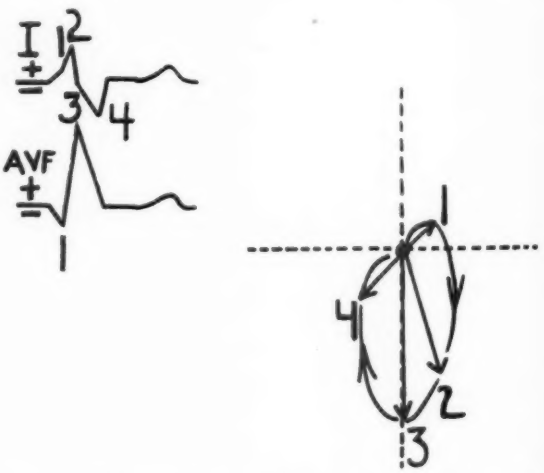

Fig. 1. Diagram showing the electrical axes (arrows) of the heart calculated from leads 1 and aVF at four instants in the cardiac cycle. When the tips of the arrows are joined by a curved line, a loop is formed. This is a vectorcardiogram.

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for all instants in the cardiac cycle, it would vary markedly from instant to instant in size and direction. Furthermore, if the tips of the electrical axes were joined, a curve or loop would be formed. This loop is a vectorcardiogram. Figure 1 shows this.

In the method just described, the vectorcardiogram obtained could be called a *frontal plane vectorcardiogram* because the extremities which are used for recording the standard and the aV leads lie on the frontal plane of the body. The frontal plane vectorcardiogram shows how the electrical axis is spreading through the body as projected on this frontal plane. However, it tells nothing about how the electrical axis is spreading through space. This defect can be remedied by obtaining a *horizontal plane vectorcardiogram* and a *sagittal plane vectorcardiogram*.

There is another way of describing the relations between vectorcardiograms and electrocardiograms. Each vectorcardiogram can be considered as a composite electrocardiogram. For example:

The *horizontal plane vectorcardiogram* can be considered a composite cardiogram of the six precordial V leads.

The *frontal plane vectorcardiogram* can be considered as a composite cardiogram of the three standard and the three aV leads.

The *sagittal plane vectorcardiogram* can be considered as a composite cardiogram of the esophageal leads.

We know that for most clinical purposes, with the important exception of the diagnosis of posterior myocardial infarction and acute massive pulmonary embolism, the precordial leads give more information than either the standard, the aV, or the esophageal leads. Similarly, we should expect to find that the horizontal vectorcardiogram gives more information than either the frontal plane vectorcardiogram or the sagittal plane vectorcardiogram. Before describing the horizontal plane vectorcardiogram and the method of deriving it, a brief description of a vectorcardiographic apparatus will be of value.

Vectorcardiographic Apparatus: Briefly, the apparatus consists of two electrocardiograph machines connected to a cathode ray or television tube. One electrocardiograph is fed into the horizontal deflecting plates of the tube; the other electrocardiograph is fed into the vertical deflecting plates of the tube (Fig. 2). The electron beam of the tube is therefore subjected to two electrical forces at right angles to each other. As a result, the electron beam describes a loop on the face of the tube. This is the vectorcardiogram. In other words, a vectorcardiogram records two electrocardiograms taken simultaneously from points on the body at right angles to each other and equidistant from the heart.

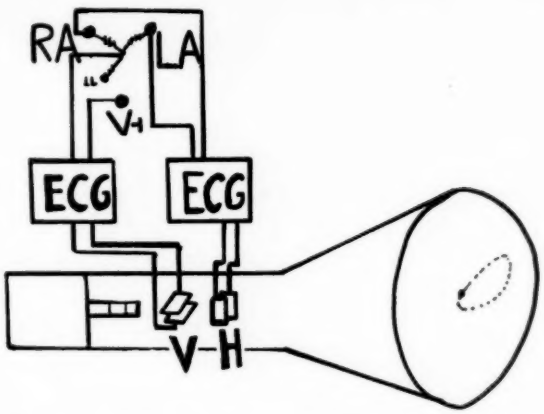

Fig. 2. Diagram of a vectorcardiograph apparatus. Two electrocardiographs (*ECG*) are fed into the horizontal (*H*) and vertical (*V*) deflecting plates of a television-like tube. The deflections of the electron beam produce a loop on the face of the tube. In the diagram, lead 1 is connected to the horizontal deflecting plate, and lead V_1 to the vertical deflecting plate. This produces a horizontal plane vectorcardiogram.

Leads for Vector Recording: There are numerous leads which can be used to record vectorcardiograms.[1,2,4] We have found the following satisfactory: *Horizontal plane vectorcardiogram*—leads 1 and V_1; *frontal plane vectorcardiogram*—leads 1 and aVF; *sagittal plane vectorcardiogram*—leads V_1 and aVF.

In Figure 2, notice that lead 1 is being fed into the horizontal deflecting plates of the tube and lead V_1 is being fed into the vertical deflecting plates of the tube. The loop which results will therefore be a horizontal plane vectorcardiogram.

The Derived Electro-Vectorcardiogram

(1) *The first step* is to use a proper coordinate system or diagram. Figure 3 shows this. Notice that the diagram is divided into four

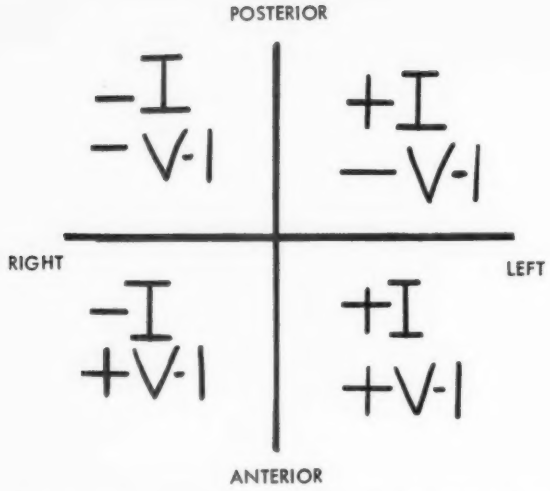

Fig. 3. Diagram used to derive a horizontal plane vectorcardiogram from leads 1 and V_1. See text for details.

quadrants, marked + and −. These signs merely indicate an upward or downward deflection of the lead. For example, the quadrant marked $+1 + V_1$ would indicate that when leads 1 and V_1 simultaneously show an upward deflection, the vector loop lies in this quadrant.

(2) *The second step* is to study the electrocardiogram and select a characteristic complex in leads 1 and V_1 in order to derive the horizontal plane vectorcardiogram.

(3) *The third step* is to note the direction of the initial deflections of the QRS in leads 1 and V_1. In Figure 4, notice that the initial deflection is upward in lead 1 and upward in lead V_1. Therefore, the first portion of the vector loop moves from its starting point into the $+1 + V_1$ quadrant.

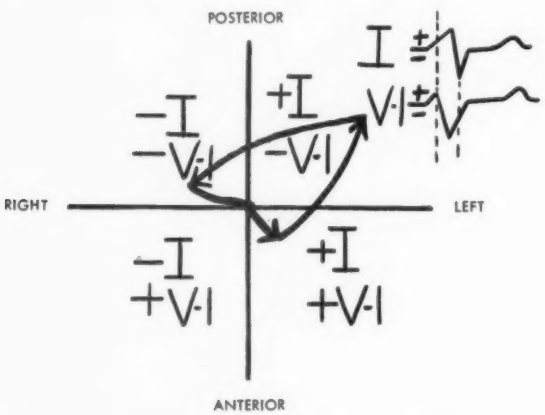

Fig. 4. A normal horizontal plane vectorcardiogram. See text for details.

(4) *The fourth step* is to note the time of onset of the major peaks of the QRS in the two leads. The time of onset of the peak of R or the nadir of S in a lead is measured from the point where the QRS begins to the peak or nadir.

(5) *The fifth step* is to use this information to determine the location and the direction of rotation of the vector loop and to draw it.

For example, in Figure 4, notice that the peak of the R wave occurs earlier in lead V_1 than in lead 1. This means that lead V_1 will become negative earlier than lead 1. More specifically, it means that lead V_1 will become negative while lead 1 is still positive. Therefore, we know that the vector loop will move into the $+1 - V_1$ quadrant. A moment later, the electrocardiogram shows that both leads are downward. Therefore, the vectorcardiographic loop must move into the $-1 - V_1$ quadrant, and then return to the starting point.

Normal Horizontal Plane Vectorcardiogram: Figure 4 shows a normal horizontal plane vectorcardiogram. It has two fundamental characteristics: (1) It shows counterclockwise rotation; and (2) it is displaced posteriorly and to the left. The reason for this is the relative size of the right and left ventricles and the way the stimulus spreads through the heart. Normally, the stimulus quickly spreads through the ventricular septum from left to right and anteriorly. This produces the normal initial anterior movement of the vector loop. A moment later, the stimulus spreads outward from endocardium to epicardium and to the left and backward through the left ventricle. Although the stimulus also is spreading outward through the right ventricle at this time, the electrical activity of the normal right ventricle is negligible compared to that of the left ventricle and can be disregarded.[1] Therefore, it is the normal outward backward spread of the stimulus through the left ventricle which dominates the normal electrocardiogram and vectorcardiogram.

The Derived Electro-Vectorcardiogram in Right Ventricular Hypertrophy

When right ventricular hypertrophy occurs, the hypertrophied right ventricle projects an-

teriorly. Therefore we should expect the horizontal plane vectorcardiogram to show anterior projection. In addition, the large muscle mass of the right ventricle also causes the horizontal plane vector loop to change in direction from counterclockwise to clockwise.

Case with Typical ECG: Figure 5 shows this.

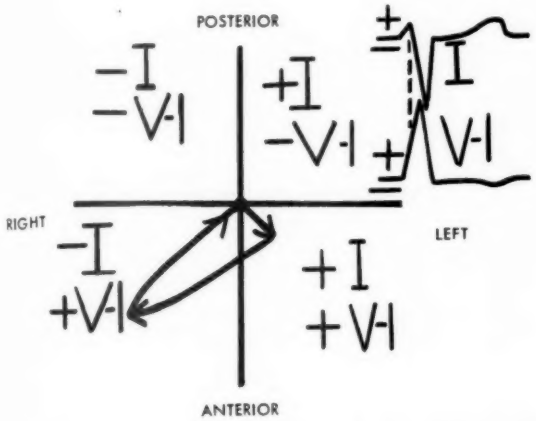

Fig. 5. Horizontal plane vectorcardiogram in a case of right ventricular hypertrophy with typical electrocardiogram. See text for details.

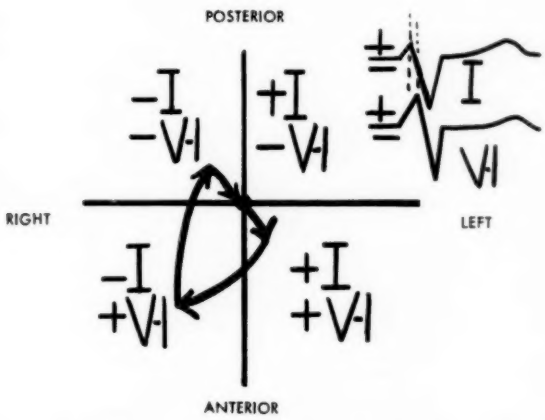

Fig. 6. Horizontal plane vectorcardiogram in a case of right ventricular hypertrophy with equivocal electrocardiogram. See text for details.

The initial deflections of both leads 1 and V_1 are upward and the initial deflection of the horizontal plane vectorcardiogram is into the $+1$ $+V_1$ quadrant. However, the peak of R in lead V_1 is delayed because of the right ventricular hypertrophy, and occurs a little later than the peak of R in lead 1. Therefore, lead V_1 is still positive when lead 1 has become negative. Therefore, the vector loop moves clockwise into the -1 $+V_1$ quadrant. Since lead V_1 is positive throughout the entire cardiac cycle, the loop remains in this -1 $+V_1$ quadrant and then returns to the starting point.

This is the typical vectorcardiographic pattern of right ventricular hypertrophy. It shows anterior displacement of the horizontal plane loop and clockwise rotation of the loop.

Case with Equivocal ECG: The electrocardiogram of Figure 5 is so typical of right ventricular hypertrophy that no diagnostic problem would arise. However, Figure 6 shows a more complex problem. Here, the tall R wave in lead V_1, characteristic of right ventricular hypertrophy, is not present. However, the derived vectorcardiogram indicates that right ventricular hypertrophy is present.

The initial deflections of both leads 1 and V_1 are upward, so the vector loop first moves into the $+1$ $+V_1$ quadrant. However, note that here also the peak of R in lead V_1 is delayed and occurs later than the peak of R in lead 1. Therefore, lead V_1 remains positive when lead 1 has become negative and the vector loop moves clockwise into the -1 $+V_1$ quadrant. A moment later, both leads 1 and V_1 are negative, and the loop moves into the -1 $-V_1$ quadrant. This loop, although differing slightly from that in Figure 5, shows the characteristic anterior displacement and clockwise rotation typical of right ventricular hypertrophy.

Summary

In a case of suspected right ventricular hypertrophy, when the electrocardiogram shows equivocal findings, the diagnosis of right ventricular hypertrophy can be confirmed by deriving the horizontal plane vectorcardiogram, and finding anterior displacement of the vector loop and clockwise rotation. The presence of a tall R in lead V_1 is the clue to the anterior displacement of the loop. The delayed peak of R in lead V_1 compared to lead 1 is the clue that clockwise rotation of the loop is present.

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Letters to the Editor

Myocardial Infarction in the Negro

Dear Sir:

The paper by Doctors Mihaly and Whiteman, "Myocardial Infarction in the Negro," in the October issue [AM. J. CARDIOL. 2: 464, 1958], was a dedicated effort. It would have been more valuable as a scientific contribution if some of the emotional content had been eliminated. It seemed to me that in the first one or two pages of their essay the authors indicated a determination to refute previous data, which is their privilege. Nonetheless, among cardiologists who have cared for negro patients both in the North and the South, there is a good deal of skepticism as to identical frequency of coronary disease in both races.

It seems to me that one aspect of the problem which has not been adequately considered in this paper is the problem of tension among southern negroes and among those living in northern cities. It is my impression that there is, somewhere in the literature of the last few years, a similar study in the case of peptic ulcer among southern Negroes and those resident in Chicago. It could be that the ideas of the authors of this paper are correct without casting reflection on the accuracy of previous observations on the same subject. Their reference to the paper of Fitzgerald and Yater with its suggestion of identical occurrence in the city of Washington, D. C., would be subject to the same reservation, since Washington and New York City have many similarities both as to race and tension.

ROBERT J. NEEDLES, M.D.
St. Petersburg, Florida

AUTHORS' REPLY

Dear Sir:

We are grateful to Dr. Needles for having recognized our paper as a dedicated effort. We are of the opinion that the value of a paper depends on the soundness of the facts presented, and the logic of the conclusions drawn from these facts. The paper was not written merely with a determination to refute previous data, but to present the historical evolution of the subject and all the facts systematically, which we considered our duty rather than privilege. We hope our paper will help dispel the skepticism of some cardiologists to which Dr. Needles refers.

Dr. Needles may be correct in presuming that tension is an important factor in coronary artery disease. Since, however, there is no way of quantitating tensions or individual reactions to them, we omitted these in a work based on documented historical facts and finite clinical data. We wish to point out that a large number of our patients—we cannot give the exact figure without re-examining our case histories—were natives of southern states and spent many if not the majority of their years in these native states. Others migrated frequently between New York City and the South. We are glad to recognize the implied suggestion of Dr. Needles that, regardless of race, tension and way of life are an index to be considered.

The paper of Fitzgerald and Yater to which Dr. Needles is presumably referring shows a white to negro ratio of 2:1. Another paper by Yater *et al.* on studies of coronary disease in army personnel, where factors of geographical origin had been neutralized of necessity, and to which we referred in our paper as a monumental work, is suggested for considered study.

JOHN MIHALY, M.D.
NEVILLE C. WHITEMAN, M.D., F.A.C.C.
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Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

Fetal Electrocardiography

SINCE the introduction of fetal electrocardiography over 50 years ago, a number of reports have appeared which suggest that it may be of value in routine obstetric practice. However, the actual clinical value of fetal electrocardiography has not been defined.

In an attempt to evaluate fetal electrocardiography from this standpoint, Drs. Edward H. G. Hon and Orvan W. Hess (Department of Obstetrics and Gynecology, Yale University School of Medicine) studied fetal electrocardiograms for two major purposes: (1) the evaluation of the fetus, when the fetal heart beat cannot be detected by auscultation; and (2) continuous monitoring of the fetal heart rate during labor for the detection of changes which may be related to fetal distress.

The patients studied for fetal life fell largely into two groups: (1) early gestation (18–20 weeks); and (2) when the fetus was full-term size but the mother was markedly obese or had hydramnios, so that the fetal heart could not be heard with a stethoscope. The diagnosis of fetal life before 20 weeks of gestation was 100 per cent accurate in the 23 patients studied. In later pregnancy, a 92 per cent accuracy was obtained in 127 patients. It should be emphasized that these figures were obtained under conditions in which the obstetrician could not hear the fetal heart beat and therefore indicate the probable value of such an instrument in routine clinical practice.

This study of fetal heart rate during labor has revealed patterns of bradycardia which are significantly different from each other so that with further experience it may be possible to differentiate "physiologic" from "pathologic" bradycardia. Clinically, it is valuable in providing an objective assessment of bradycardia and arrhythmia noted during labor. The significance of the various fetal heart rate patterns is not yet clear, but the establishment of continuous objective measurements of fetal heart rate patterns during labor will aid in definition of the normal and thereby provide a background for evaluation of the abnormal.

The Clinical Use of Hypothermia Following Cardiac Arrest

FOLLOWING cardiac arrest, restoration of the heart beat by massage is frequently possible. However, when circulation is arrested for more than four minutes, central nervous system injury usually prevents survival of the patient. The clinical picture in such patients is one of increasing cerebral swelling and finally death. The observation that generalized hypothermia reduces cerebral swelling, and reports that hypothermia appears to be beneficial in other types of central nervous system injury, suggested to Drs. G. Rainey Williams and Frank C. Spencer (University of Oklahoma Medical Center, Oklahoma City) that hypothermia might be helpful in treating patients with evidence of brain damage following cardiac resuscitation.

Four patients were treated between January and November, 1957. Two were adults and

two were children. Cardiac arrest occurred unexpectedly, and was due to a reversible cause in each case. In each instance, the patient was outside an operating or recovery room area when arrest was detected. Immediate thoracotomy and cardiac massage were carried out, and in all cases the surgeon estimated that circulation was arrested for at least five minutes. Following closure of the chest the patients were deeply unconscious, with dilated, fixed pupils. Hypothermia was instituted immediately using a circulating water mattress.* Tracheostomy was performed in two cases. Extensor spasm and hyperreflexia were present in the first few hours, but neurologic improvement was noted beginning in 18 to 48 hours. Hypothermia was discontinued when definite neurologic improvement was demonstrated (from 24 to 72 hours). In three patients complete recovery occurred. In the fourth patient a moderately severe visual defect was present which continued to improve until six months after injury.

In anoxic injury, progressive cerebral swelling appears to be the process responsible for delayed death. The mechanism by which hypothermia modifies brain swelling is not known. Zimmerman and Spencer have demonstrated that hypothermia, following circulatory arrest, results in an increased percentage of survivors in dogs. Furthermore, the previous rarity of survivors of cardiac arrest occurring outside the operating or recovery room adds significance to the reported group of cases.

The following points are considered important: Hypothermia should be started immediately following cardiac arrest when there is evidence of central nervous system injury. Temperature is maintained at 32°–34°C until there is good evidence of neurologic improvement. Tracheostomy is helpful. General maintenance is, of course, essential.

*Hypo-hyper Unit, Thermorite Products Corporation, Buffalo, New York.

Cardiac Resuscitation

Edited by PALUEL J. FLAGG, M.D., F.A.C.C.*

New York, New York

Man in Vivo

A Three-Dimensional View of Resuscitation Stressing the Integration of Form, Function, and Timing

IF WE ARE to understand living man in health and under the stress of accident and disease, we must accept the concept of completely integrated form (what), function (how), and timing (when).

Anatomy, without cellular and somatic function, is nothing more than a disintegrating cadaver. Physiology, without biochemical timing, is but tissue activity responding to external stimuli. Timing operates through blood and cellular chemistry. It synchronizes the anatomic, the physiologic, and the biochemical. The result is normal healthy man.†

It would be out of place, elementary, and repetitious to rehearse details of the basic sciences, anatomy, and physiology. However, the third dimension of this trilogy, timing, is something not sufficiently stressed and most likely to be overlooked. Yet, as related to respirocardiac resuscitation, it often assumes first place. The cardiologist is accustomed to view his problems in terms of hours, days, weeks, or months. Here, we face emergencies which turn on minutes.

Timing operates by determining the instant, the degree, and the duration of function. Its recognition allows the instantaneous freezing of the fluidity of function (as though a motion picture had stopped at one frame). It permits of a precise diagnosis or the application of a desirable act, as it were in functional transit. The effect of a gas or a drug either progresses or retrogresses, it is never static. Timing determines the correct instant of effect or action. Form and function can be taught; timing must be experienced.

REVIEW OF NORMAL RESPIROCARDIAC FUNCTION

Let us imagine an integration and activation of the conventionally isolated anatomic form and physiologic function through a fluoroscopic view of the total living organism. Customary equipment has been amplified by a new, deep penetration and accurate color rendition which permits a view of all living structures in the depth of tissues and organs. Nerve impulses, their origin, intensity, direction, and duration become visible as moving blue illuminations. Ganglia and nerve centers glow steadily, nerve impulses moving from and to these centers. A flashback allows us, now and then, a glimpse of embryonic organic development.

RESPIRATORY FUNCTION

First, we note that the respiratory system acts precisely in accordance with the blue impulses moving to and from the glowing center in the medulla and from the sympathetic ganglia; these appear as a chain of lights within the cord

* President, National Resuscitation Society.

† For the sake of simplicity, man is considered herein merely as a living animal. He is not regarded as a human being with all the spiritual and intellectual faculties which dissociate him from the lower animals. This position is justified by the fact that in unconscious man the intellectual faculties are in abeyance.

and along the sides of the spinal column. The lungs are suspended in their bony cage. Through phrenic stimulation of the intercostals, the ribs, attached to the vertebrae behind and the sternum in front, rise like the handle of a pail in inspiration, increasing the internal diameter of the chest. Simultaneously, the diaphragm contracts, depressing the floor of the pulmonary space and increasing its vertical diameter. The visceral pleura, moving smoothly 3 or 4 inches against the parietal, follows the negative intrapleural pressure created by the enlargement of the chest cavity. As the lungs expand, air is sucked into the trachea, bronchi, and bronchioles, altering the gases of the alveoli by diffusion. As pressure increases, the nerve endings of the vagus in the alveoli begin to glow. Blue impulses pass back to the parasympathetic ganglia and inspiration is arrested (Hering-Breuer reflex). Intrapleural negative pressure is reduced. Intrapulmonary pressure is increased. Expiration takes place as a relaxation of the diaphragm, intercostal muscles, and bronchi, assisted by the contraction of the bronchioles. Inhaled air escapes through bronchi, trachea, and upper airway.

Reduced pressure in the alveoli, increased concentration of CO_2 in the blood, and the blue afferent impulses from the aortic and carotid bodies pass to the respiratory center, again initiating the positive act of inspiration. The suction effort of inspiration is a powerful factor in moving the dark venous blood out of the capillary bed to the large veins of the neck and into the vena cava. Indeed, during the peak of inspiration the jugular veins are seen to collapse as a result of this suction effect.

Granted this normal and necessary aid to the movement of the blood stream, the handicap of sedatives and anesthetic drugs, which frequently depress the respiratory act to complete apnea, can readily be appreciated. Furthermore, barbiturates eliminate the normally stimulating effect of carbon dioxide. It is noted that changes in the alveolar air take place through diffusion, rather than by mechanical movement.

Cardiovascular Function: As we view the crimson, pulsating heart, we note a darker stream entering the right side, passing immediately from auricle to ventricle, thence to the pulmonary artery. The eye follows this dark, pulsating stream as it bifurcates and enters the hilum of each lung. We see it ramify through lobes and lobules, terminating in the alveolar capillaries. The blood in these capillaries is now separated from the quiet, alveolar air by the microscopic thickness of a single cell. As the dark blood in the venules enters the capillaries it changes instantly to bright red. This oxygenated blood leaves promptly by venules. These shortly become veins, uniting to form the pulmonary vein, which discharges its contents into the left auricle. This bright, oxygenated blood, at a pressure of only a few mm Hg, is squeezed into the left ventricle. The auriculoventricular valve closes with the familiar "lubb." Here pressure conditions are instantly and greatly increased. The ventricle contracts powerfully. The systemic blood pressure in the aorta is overcome. Ventricular contraction completed, the aortic valve closes sharply with the familiar "dub." It is well to pause a moment to reflect upon the importance of the rate, the rhythm, and the power of the left ventricular beat. Upon its integrity depend consciousness and life. With loss of rhythm and power for even a minute, as in ventricular fibrillation, the sustained column of blood pressure immediately falls, stagnant hypoxia develops, unconsciousness ensues, and, if these are unrelieved, death follows.

Near the source of the maximum aortic pressure arise the carotid and axillary arteries. The former supply the higher centers with fully oxygenated blood. Compression of the aorta between the carotid and axillary arteries, when employing cardiac massage in cardiac arrest, assists in concentrating the massaged blood stream to the medulla.

Peripheral Vascular Bed: The total vascular arterial bed is alive, not only by virtue of the rhythmically pulsating heart but by reason of the contraction and the dilatation of the arterial lumen, activated by impulses we observe passing from the sympathetic system, the aortic body, and carotid sinuses. These chemoreceptors, responding to increased CO_2, lactic acid, and sympathin, respond promptly by stimulating constriction of the arterial lumen. As arterioles become capillaries, pressure within them disappears. In this vast capillary bed, where blood

vessel walls consist of a single layer of flattened cells, where the lumen is so small that the red blood cells pass through in single file, lurks drama, the tragedy of life and death. Indeed, the great cardiovascular-respiratory systems exist for the safety and the life of the cells in the capillary bed. Here, basic forms of anoxia, which cripple and destroy the organism, are clearly seen, e.g., *anemic anoxia*—too few red blood cells, too little hemoglobin, hemoglobin neutralized by carbon monoxide, or oxyhemoglobin locked up in the cell because of too little CO_2; *histotoxic anoxia*—tissue cells poisoned by alcohol, sulfur drugs, the gamma rays of atomic radiation, or by cyanides, which prevent them from utilizing the oxygen passing by; *stagnant anoxia*—circulatory depression from cardiac decompensation, loss of muscle tone from spinal anesthesia or through overventilation (excessive use of soda lime absorption); *anoxic anoxia*—oxygen deficiency from its various causes, sudden allergic or anaphylactic reactions in which the plasma contained in the capillaries seeps through the retaining wall, flooding and strangulating the tissue cells.

Arterial capillaries become venules by virtue of their contents. Changes in the color of the blood are due exclusively to variations in the oxyhemoglobin content. Carbon dioxide has no effect on the color. The dark blood in the venules and veins, propelled by muscle tone and movements supported by valves, flows into the great vessels. Progress is accelerated by the negative pressure induced by the act of inspiration. Finally, at a low pressure of 2 or 3 mm Hg, the vena cava empties its contents into the right auricle.

Effects of Suspension of Respiratory Function

Since the three-dimensional view, which we are attempting to stress, is the only realistic background through which we may study hypoxia in accident and disease, we may now attempt to describe the development of a simple physiologic event in time, that of voluntary holding of the breath. We shall proceed from this point to the catastrophic effect of total artificial respiratory obstruction by mechanical means.

Voluntary Breath-Holding: Biochemical rebellion against cessation of a normal function becomes apparent when a voluntary effort is made to stop breathing. The stop watch is at zero. Respiration ceases. The accumulating CO_2, the slight increase in blood pressure, acting on the aortic and carotid chemoreceptors, the distention of the alveolar sacs, flashing afferent signals to the respiratory center and the diminished oxygen in the circulating blood, all increase very rapidly the *besoin de respire*, the need to breathe—40 seconds, 45 seconds, the need becomes urgent*—finally with an explosive effort, automatic respiration breaks through. Deep rapid respirations ensue. The accumulated CO_2 is immediately ventilated out. Hyperpnea, increased respirations, as well as apnea from rapid breathing, may be induced at will. Unconsciousness and apnea from overbreathing are frequently seen in anxiety, fear, etc., and may result in syncope from CO_2 loss. Swimmers' cramps are explained by acapnia. Hypoxia, without cyanosis, is not uncommon, where overventilation has reduced the CO_2 to a point where the oxyhemoglobin will not release its oxygen (Bohr phenomenon).

At the turn of the century, Haldane, Yandell Henderson and others stressed the vital role of CO_2. This concept became well established. Since then, methods to overcome the dyspnea of rebreathing and to economize in the use of anesthetic agents have resulted in the wide use of the so-called CO_2 absorption technic. Once more, CO_2 is regarded as a poison to be eliminated as rapidly as possible. The results are not surprising: loss of muscle tone, apnea, anemic anoxia, and fall in blood pressure. The open drop method of ether anesthesia frequently resulting in shock from overventilation has now been replaced by the same effect induced by soda-lime absorption.

The experiment just made to cease breathing indicates the reaction of the organism when a voluntary attempt is made to suspend a vital function. It is an index of the physiologic demand for perfect correlation of function. If now suppression of function is continued by accidental mechanical means, that is, beyond the limits of voluntary control, consciousness itself is promptly lost and tragic effects rapidly follow.

* 60 seconds, 5.5 liters of blood have circulated through the body. The second circulation begins.

Mechanical Respiratory Obstruction: Accidental mechanical tracheal obstruction will now be superimposed upon the voluntary attempt to hold the breath. Once again respiration ceases. Just before voluntary respiration breaks through, that is at 45 seconds, regurgitated stomach contents obstruct the trachea completely. Ineffective respiratory efforts occur. Consciousness is confused, then lost altogether. Excitement develops with general muscular and facial evidences of extreme distress. The clonic jerky movements of the muscles shortly become tonic (rigidity). The jaw is clenched; the extremities are rigid. Cyanosis of the lips, conjunctivae, and skin develops. The pulse is full and bounding; blood pressure increases. CO_2, lactic acid, and sympathin accumulate in the blood. The normal suction action of respiration ceases, and blood dams back into the alveolar capillaries, the pulmonary artery, and the right heart. The coronary arteries become engorged. The heart dilates. Hypoxia sensitizes the heart muscle to arrhythmia and retarded beats. Stagnant hypoxia develops in the tissue capillary beds. Dark red blood cells escape from the capillary lumen; they cause superficial and deep ecchymoses. Cerebral and visceral tissue hemorrhages occur. The sympathetic and parasympathetic ganglia glow with a dull luminosity. Afferent and efferent impulses along nerve trunks overlap and appear to be short-circuited.

As hypoxia proceeds, muscle relaxation follows muscle spasm. Muscle tone disappears. The limbs and the jaw relax. The upper airway and larynx offer no resistance to exposure. Accompanying the over-all relaxation, the intercostals and the diaphragm become flaccid. Parasympathetic impulses through the vagus slow the dilated heart. The cardiac muscle loses force and blood pressure drops. The heart stands still. As cerebral anoxia continues, the glowing intensity of the respiratory center lessens, the delicate nerve cells will soon suffer irreparable damage. It is now four minutes since the initial cessation of the respiration. The phenomenon which Corrylos demonstrated in submerged dogs many years ago is seen in action: initial apnea, one minute; dyspnea, one minute; terminal apnea, one minute; apparent death, one minute.

Now, we have arrived at the last minute—apparent death. Perhaps 60 seconds remain to prevent permanent cerebral damage and death. While the heart has ceased to beat, life may still be saved thanks to the pioneering work of Dr. Claude S. Beck.

The next article to appear in the section on Cardiac Resuscitation will be the first of a series dealing with the history, the physiology, and the use of cardiac drugs and instrumentation in the treatment of arrested and fibrillating heart.

NOTE: The course in Respiro-Cardiac Resuscitation described in the December issue of the Journal will be presented in New York City, February 5–6, 1959. A special out-of-town course will take place in Indianapolis on January 24-25, 1959. For information address Secretary, N. R. S., Inc., 2 East 63 St., New York 21, N.Y.

College News

1959 ANNUAL MEETING

The Eighth Annual Meeting of the American College of Cardiology will be held on May 25–29, 1959 inclusive at the Benjamin Franklin Hotel, Philadelphia. Dr. Robert P. Glover has been appointed Local Convention Chairman.

Call for Abstracts of Papers

All members of the College are requested to submit or urge their associates to submit 250 word abstracts of original scientific studies in the field of cardiovascular diseases for the Annual Meeting of the College in Philadelphia on May 25–29, 1959. These abstracts are to be mailed to the Chairman of the Program Committee, Dr. John S. LaDue, 115 East 61st Street, New York 21, N. Y., for consideration by the Program Committee.

Eight papers will be selected for presentation by members of the College at the Annual Meeting. Abstracts must be submitted by February 15, 1959. Your cooperation is essential to our having a good meeting.

Announcements

The American Society for the Study of Arteriosclerosis

At the last Annual Meeting of the American Society for the Study of Arteriosclerosis the following officers were elected:

President ..... J. C. PATERSON, M.D.
London, Ontario, Can.
Vice President ..... FORREST E. KENDALL, PH.D.
New York, N.Y.
Secretary-Treasurer ..... O. J. POLLAK, M.D., PH.D.
Dover, Del.

Directors until 1961

IVAN DERAY FRANTZ, M.D.
Minneapolis, Minn.
JEREMIAH STAMLER, M.D.
Chicago, Ill.

Directors until 1960

JOSEPH H. BRAGDON, M.D.
Bethesda, Md.
D. B. ZILVERSMIT, PH.D.
Memphis, Tenn.

Directors until 1959

ROBERT H. FURMAN, M.D.
Oklahoma City, Okla.
ANCEL KEYS, PH.D.
Minneapolis, Minn.